RADIOLOGY

A MONTHLY JOURNAL DEVOTED TO CLINICAL RADIOLOGY AND ALLIED SCIENCES

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RADIOLOGY

A MONTHLY PUBLICATION DEVOTED TO CLINICAL RADIOLOGY AND ALLIED SCIENCES

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PUBLISHED BY THE RADIOLOGICAL SOCIETY OF NORTH AMERICA

Vol. 51 OCTOBER 1948 No. 4

Radiology: Its Twenty-Fifth Anniversary

Every successful endeavor owes much to the past. The strength of today's structure depends in large part upon the foundation laid by the workers of yesterday. The large and influential Radiological Society of North America and its official publication, RADIOLOGY, are no exceptions to this rule. Today they look back with pride and gratitude upon those to whose wisdom and foresight they owe so much.

The year 1948 marks the twenty-fifth anniversary of the founding of RADIOLOGY, but its beginnings go still further back. Any adequate account of its growth and development must start with the founding of the society which it represents and with whose history it is so closely associated.

During the early years of the present century, organized radiology in this country was represented by the American Roentgen Ray Society. Most of the meetings of that body, however, were held in the east, and because of this and the feeling that its membership requirements were somewhat over-restrictive, a new organization, the Western Roentgen Society, later to become the Radiological Society of North America, was formed. Of this new society, Dr. B. H. Orndoff, its president in 1918, wrote as follows: "Many years ago a feeling arose in the minds of roentgenologists of the western part of the United States that an organization, constructed on democratic principles and dedicated to the study and practical application of the science should be established. This feeling expanded almost unconsciously into a demand for an organization, and finally culminated in the year 1915, when roentgenologists from seventeen different states of the middle west and south assembled in Chicago and pledged themselves as charter members of an organization to be known as the Western Roentgen Society."

The new society, based on broad democratic principles, made an immediate appeal to the increasing number of men who were interested in roentgenology, and within three years its enrollment had reached 472, representing 38 states. It having thus been clearly demonstrated that the membership could not be limited regionally, the decision was reached at the November 1918 meeting, in Chicago, to enlarge the scope of the organization and in token of this to change the name to the Radiological Society of North America. The brilliant history of this great organization cannot be detailed here. It should be said, however, that it has steadily increased in size and scientific importance until it is the largest and certainly one of the most influential radiological societies of the world today.

At the 1917 meeting of the Western Roentgen Society the demand for an official journal found expression, and such a publication was guaranteed by the officers of the Society. Thus was born the *Journal of Roentgenology*, which, under the editorship of Dr. Bundy Allen, appeared quarterly during 1918 and 1919. Radiologists, in their strongly established position today, will find it hard to realize the magnitude of

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THE JOURNAL OF ROENTGENOLOGY

PUBLISHED BY THE SOCIETY

IOWA CITY, U. S. A.

Bundy Allen, M.D.

Albert F. Tyler, M.D.

this pioneer publication effort with a small membership and inadequate financial resources. Its sponsors deserve the most generous praise for accomplishing the seemingly impossible.

In 1920 the name of the publication was changed to the *Journal of Radiology*, with Dr. Allen continuing as editor and Dr. Orndoff as associate editor. Shortly after this, in order to develop a stronger financial background, it was decided to establish an independent publishing company. The journal remained the official publication of the Society but was actually controlled by the members who subscribed to stock in the Radiological Publishing Co., a non-profit-making organization. Under the new regime, the publication office was later removed to Omaha, Nebr., and in January 1922 Dr. A. F. Tyler succeeded Dr. Allen as editor.

It was not long before the disadvantages of this arrangement became apparent, and members of the Society realized that they were actually without control of their own official journal. Steps were taken to change this, and as a result direct control was again returned to the Society.

Following this episode, the Radiological Society of North America in executive session made certain amendments to its Constitution and By-Laws, whereby it definitely assumed publication of its own journal—RADIOLOGY—under the supervision of a Publication Committee to be appointed by the President of the Society for a term of three years. The first issue of RADIOLOGY, a direct successor of the *Journal of Roentgenology* and the *Journal of Radiology*, appeared in September 1923, under the editorship of Dr. M. J. Hubeny.

Dr. Hubeny continued as editor until 1931 and during this time RADIOLOGY increased rapidly in scientific importance, as well as reflecting the development of the Radiological Society of North America. The editorship was continued after 1931 by Dr. Leon J. Menville, who not only main-

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THE JOURNAL OF RADIOLOGY

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OF NORTH AMERICA

IOWA CITY, U. S. A.

Maximilian J. Hubeny, M.D.

Leon J. Menville, M.D.

tained the journal's former prestige but continued to add to it in every possible way. When Dr. Menville resigned in January 1941, on the occasion of his elevation to the presidency of the Radiological Society of North America, the present editor was appointed.

In 1930 the Radiological Society of North America was offered large subsidies by the Chemical Foundation, which desired an outlet for the complete publication of articles and abstracts of the world literature on cancer. Thus began a rapid expansion of RADIOLOGY to a size undreamed of by its founders. After several years the Society felt that its direct control of the journal was again jeopardized and it reassumed the complete financial responsibility for the publication, which it continues to bear. Its success in this undertaking is due in large part to the wise management of Dr. Donald S. Childs. Dr. Childs assumed the office of business manager in 1931, bringing to the task a combination of imagination and efficiency that has played a large part in the development of RADIOLOGY, tiding it over the difficult years of the depression and building up the circulation to its present gratifying proportions.

As one looks through the volumes of RADIOLOGY over the quarter of a century of its existence, he finds reflected there the progress that has been made in roentgen diagnosis and radiotherapy during that period. The diagnosis of gallbladder disease is a case in point. Carman, MacCarty, and Camp, in a paper published early in 1924, raised the question whether the results of examination for disease of the gallbladder as then conducted warranted the time and expense required. Exactly a year later came a paper by Graham, Cole, and Copher on "Roentgen Visualization of the Gallbladder by the Use of Intravenous Injection of Sodium Tetrabromphenolphthalein." By September 1925, articles had begun to appear on

the oral administration of tetraiodophenolphthalein, which had replaced the compound originally used by Graham and his associates, and in the following years reports of series of cases thus examined multiplied as the procedure became routine. The latest developments in this field are illustrated by the group of papers on Priodax appearing in 1944 and followed by reports of the use of this new medium in large numbers of cases as it has become more popular.

In like manner one might trace the development of myelography from the paper by Sicard and Forestier in 1926, shortly after the introduction of lipiodol as a contrast medium, to the publication in 1944 of the researches of Strain, Ramsey, and their associates at the University of Rochester on pantopaque. The progress of bronchography, pyelography, venography, angiography, body section roentgenography, and other special technics might be similarly followed.

In the matter of therapy the years have seen an increasing application of the higher voltages. This too is reflected in the pages of RADIOLOGY. The Report of the Standardization Committee on the Measurement of Dose in Roentgen Therapy, with a useful glossary, published in 1940, deserves special mention, as does the Report of the Combined Standardization Committees of the American Roentgen Ray Society and the Radiological Society of North America, in 1946, on various phases of protection. To single out for attention any individual papers is perhaps an unwise, not to say a hazardous, undertaking, but in view of their significance for the future, reference should surely be made to the Cyclotron Symposium published in 1942, to the papers by Kerst and his associates on the Betatron in 1943, and to the Plutonium Project papers in 1947.

An early editorial in RADIOLOGY calls attention to the important matter of apparatus. It begins: "The relation existing between radiologists and the manufacturers of radium applicators, deep therapy apparatus, tubes, films, and the host of agents through the instrumentality of which a radiologist makes his examinations or administers his treatments is a peculiarly close one.... There can be no sharp line drawn between those who devise and those who use." Any comment, therefore, on the technical advances set forth in the pages of RADIOLOGY from 1923 to 1948 must include a mention of its advertisers. The advertising pages are in themselves a record of achievement which accounts in no small measure for the development of the science of radiology to its present high standing among the specialties.

A feature of RADIOLOGY from its inception has been the publication of abstracts of current medical literature. The extent of this service has fluctuated somewhat over the years, but we believe that today it offers a comprehensive coverage of the radiological literature of the world, including all the important foreign radiological journals and a long list of specialty and regional journals in the United States. Through the voluntary service of radiologists from New England to California, there has been built up an abstract staff which has made possible the maintenance of a high standard of excellence in this department.

At least two special projects in connection with RADIOLOGY call for mention before this history can be considered complete. In 1943 there was issued the Twenty-Year Cumulative Index, which this year has been supplemented by a Five-Year Index covering 1943 to 1947, inclusive. In 1947 the publication of Spanish summaries of all original papers as they appear each month became a regular feature of the journal.

In 1945 a special issue of RADIOLOGY marking the anniversary of Roentgen's discovery was devoted to recounting the origin and development of the science of radiology over a period of fifty years. That RADIOLOGY, the journal, covering a period half as long, has made some contribution to that development we cannot doubt. That it may continue to do so in increasing measure we can but hope.

Idiopathic Pulmonary Fibrosis: Roentgenologic Findings[1]

LAURENCE L. ROBBINS, M.D.

Boston, Mass.

IDIOPATHIC PULMONARY fibrosis is a rare disease. The present paper deals with its roentgenologic appearance and with those conditions which may be concerned in the differential diagnosis. The radiologist, in order to make an accurate diagnosis, must be familiar with the clinical findings as well as with the roentgen appearance of the shadows cast by the pathologic process. To this end close co-operation with the pathologist and the clinician is essential.

A brief review of the literature discloses numerous known causes of pulmonary fibrosis, as well as an occasional reference to fibrosis of unknown etiology (3). Inflammatory processes, such as tuberculosis, bronchiectasis, and even syphilis (2), have been described as the etiologic factors in certain cases. Radiation (11) is known to produce fibrosis in the lung; asthma, in certain instances, will go on to the development of severe emphysema with a considerable amount of fibrosis; pneumoconiosis (9) is another variant of the condition that has well understood causative factors. Pulmonary fibrosis is associated also with rarer conditions, such as Raynaud's disease (6), scleroderma (8), and periarteritis nodosa, probably representing a part of the disease. After the known causes have been enumerated, however, a small group of cases remains in which no one factor to which the changes can be attributed is found. These cases consequently fall into the classification of idiopathic pulmonary fibrosis (1, 3, 5).

The roentgenologic appearance of idiopathic pulmonary fibrosis is somewhat similar to that of fibrosis from various known causes, and the diagnosis can be made only after correlating the roentgen and clinical findings with the known pathology of similar cases. Considerable emphysema is usually associated with well developed fibrosis, and in many instances cor pulmonale is the final picture (10).

TECHNIC OF ROENTGEN EXAMINATION

For any examination of the chest, fluoroscopy is important; in pulmonary fibrosis it is more than usually vital. Variations from normal in the motion of the diaphragm may determine the diagnosis. The expiratory motion, normally somewhat less rapid than the inspiratory, shows a definite lag in patients with varying degrees of idiopathic fibrosis and emphysema. Diaphragmatic motion gradually decreases until, late in the disease, there may be almost none; this, however, is a more frequent occurrence in cases in which emphysema rather than fibrosis predominates. During fluoroscopy, also, localized areas of emphysema may be detected, as may a tendency to fixation of the pulmonary shadows in the lung fields. Paradoxical motion of the mediastinum on inspiration is a sign well known to keen observers, but one that is seldom emphasized in present-day writing. During inspiration, there is definite, transitory widening of the mediastinum instead of the usual diminution in width.

The conventional postero-anterior roentgenogram often gives a large amount of information, but it is essential that views in other projections be available for further study to determine the presence of tiny blebs, which frequently are seen only along the pleural surfaces. The lateral view, or the oblique projections, will serve this purpose. In a few instances, a film taken with the grid or with the Potter-Bucky diaphragm may more clearly demonstrate the lesion, but in most cases this type of film is not necessary.

[1] From the Department of Radiology, Massachusetts General Hospital, Boston, Mass. Presented at the Thirty-third Annual Meeting of the Radiological Society of North America, Boston, Mass., Nov. 30–Dec. 5, 1947.

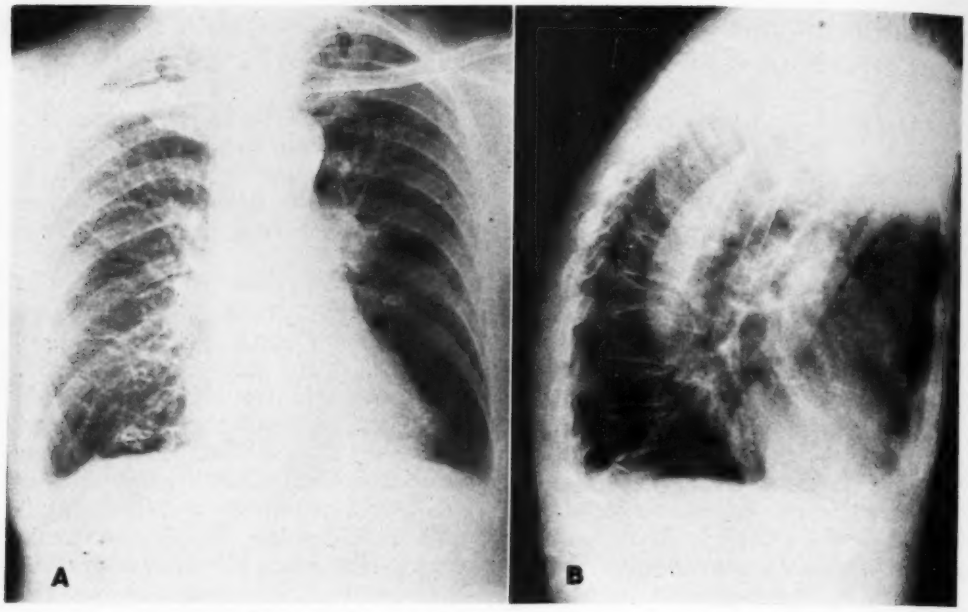

Fig. 1. Early pulmonary fibrosis and emphysema. A. Note the slight prominence of the markings in the lung fields. In the right lower chest there are linear shadows consistent with margins of blebs. The left lung field appears to be more aerated than the right, probably due to greater emphysema. B. A lateral view shows the deep anteroposterior diameter of the chest as well as the linear shadows. The flattening of the diaphragm is apparent in both projections; fluoroscopically, its motion was surprisingly good.

Clinical: The patient, a man of 73 years, entered the hospital because of swelling of the ankles and shortness of breath. Five years before, he had begun to experience dyspnea on exertion, followed two years later by moderate swelling of the ankles; relieved by digitalis. No history of occupational hazard, hypertension, or asthma.

Autopsy: Considerable fibrosis and emphysema of lungs, with numerous blebs in left upper lobe; slight right ventricular hypertrophy.

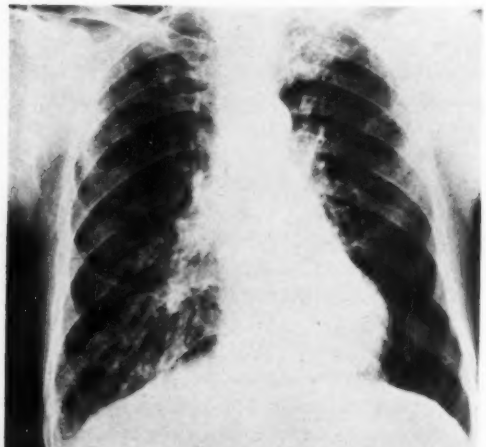

Fig. 2. Mild pulmonary fibrosis and emphysema. Fluoroscopy showed definite limitation of expiratory motion of the diaphragm. There is an increase in the markings throughout the lungs, and the walls of numerous blebs are apparent.

Clinical: The patient, a 64-year-old man, was admitted to the hospital because of acute urinary retention, and transurethral resection for carcinoma of the prostate was done. Dyspnea was the only pulmonary symptom. The patient had been a locomotive engineer; there was no known etiologic factor for the fibrosis.

Autopsy: Pulmonary emphysema and fibrosis. Evidence of old rheumatic heart disease involving the mitral, aortic, and tricuspid valves.

Laminagraphy may bring out small blebs with greater clarity than do other roentgenograms. Bronchography may reveal any bronchiectasis that is present, but this bronchiectasis is usually no greater than would be expected with the degree of emphysema that is evident and probably is not of any clinical significance. Seldom will the oil enter the blebs.

The points of greatest value in the tech-

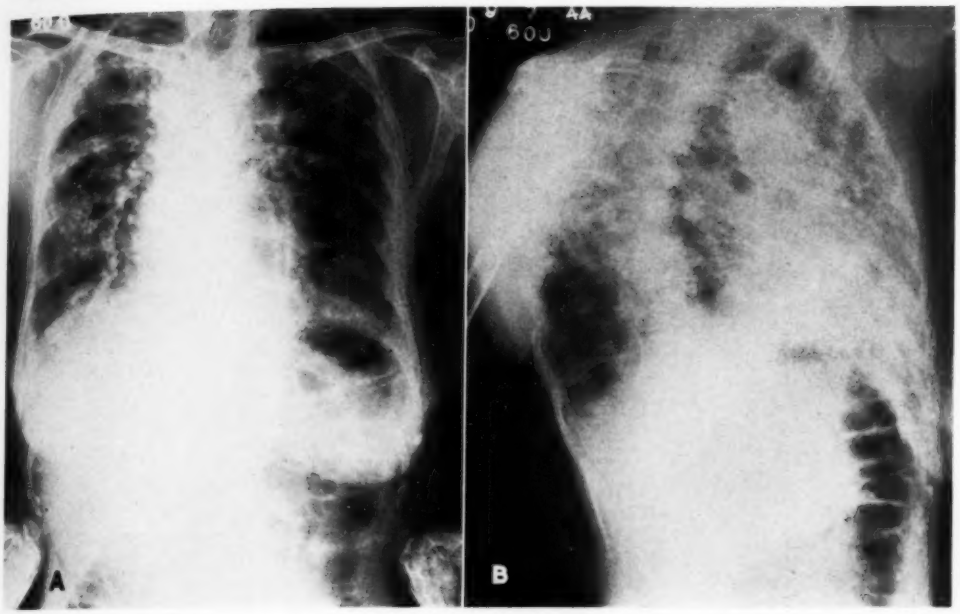

Fig. 3. Advanced pulmonary fibrosis and emphysema. Diffuse increase in markings is apparent throughout the lung fields, but the shadows are less sharply defined and somewhat larger than those in Figures 1 and 2, probably due to fusion. Interspersed with the fibrosis are areas of rarefaction consistent with blebs. The diaphragm is low in position and, although the trachea is angulated, it appears to be widened in the upper portion of the chest. Note the calcified shadows in the neck, abdomen, and left breast.

Clinical: The patient, a woman of 62, gave a history of a persistent cough for several years. Nine months before admission she had an acute episode called "influenza." Following recovery, she was well, except for chronic cough, until three months prior to entry, when she became dyspneic on exertion. The dyspnea grew progressively worse, until she was barely able to walk. The patient had had tuberculosis involving lymph nodes in the neck, axillae, groin, and left breast at the age of twenty-two; three years later, she had had tuberculous peritonitis. There had been no known pulmonary involvement. In the hospital, she became increasingly dyspneic; peripheral edema and cyanosis developed, and death ensued.

Autopsy: Pulmonary fibrosis and emphysema.

(Although there was no recognized pulmonary tuberculosis, the history suggests that a tuberculous infection was the cause of the pulmonary lesions. This could not be proved, however.)

nical part of an examination which attempts to determine the presence of pulmonary fibrosis are: (*a*) fluoroscopy, (*b*) a postero-anterior roentgenogram, and (*c*) a lateral view, or both oblique projections.

ROENTGEN APPEARANCE

Early in the course of that form of disease in which fibrosis predominates, there is a slight prominence of the markings throughout the lung fields; this may be the only recognizable abnormality. Inasmuch as most of these changes are peribronchial or perivascular, it is extremely difficult to differentiate them from slightly enlarged blood vessels or lymphatic channels. In rare instances (Fig. 1), a few blebs or localized areas of emphysema may be apparent. The diaphragm may show slight limitation of motion but often will move fairly normally.

When the disease is moderately advanced, the roentgenogram shows further increase in the size of the linear shadows, with a tendency to some nodularity (Fig. 2). As the condition progresses, the sharp definition of these shadows becomes less marked. The motion of the diaphragm is usually impaired, and the areas of emphysema are more pronounced.

In the far advanced stage, there is marked thickening of the strand-like shadows throughout, since many have become fused; they are interspersed with areas of emphysema (Fig. 3). In the majority of cases, the walls of emphysematous blebs

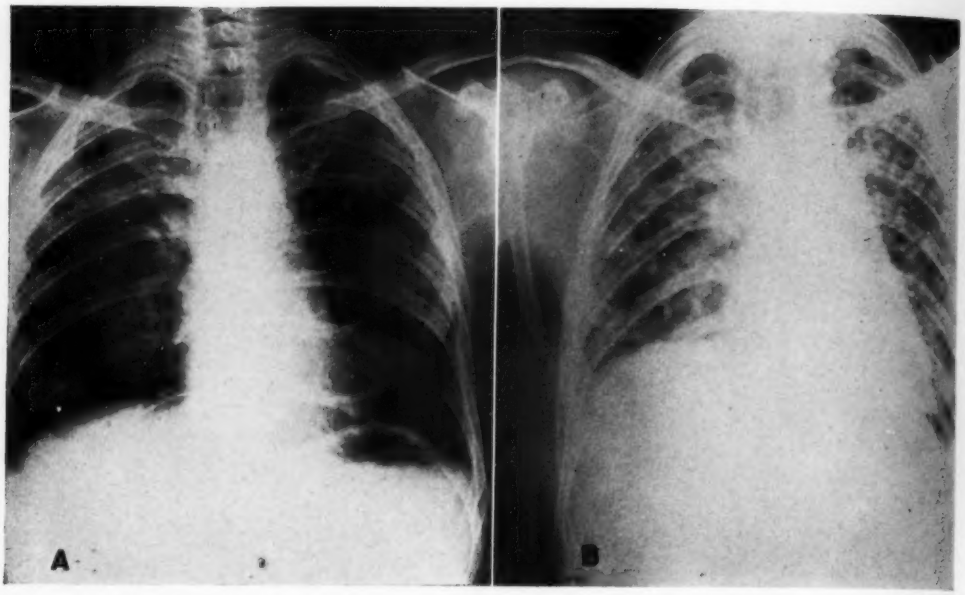

Fig. 4. Development of pulmonary fibrosis. A. The brightness of the lung fields with relatively few markings is a striking feature. There is slight prominence of markings in the upper lung fields. The trachea is widened. B. Two years later. Note the enormous fibrotic strands diffusely involving both lung fields, with intervening areas of rarefaction resembling emphysematous blebs. The width of the trachea is increased over normal.

Clinical: The patient, a 34-year-old man, had a hacking cough for six months before his first admission. The cough became increasingly productive of whitish mucus and there was gradual loss of weight and energy. A diagnosis of pulmonary fibrosis was made and the patient was followed for about three years, during which time the dyspnea grew progressively severe. Death occurred twenty-four hours after the onset of what was apparently an acute bronchopneumonic process. The patient was an auditor by profession. No etiologic factors were ever demonstrated.

Autopsy: Pulmonary fibrosis and emphysema with bronchopneumonia.

are clearly demonstrated. The blebs, which are a typical accompaniment of fibrosis, contain no lung markings and are characteristically thin-walled; they vary from a few millimeters to three or four centimeters in diameter. (Bullae and pneumatoceles are of similar nature. Bullae are numerous and thin-walled but are larger than blebs; pneumatoceles, as a rule, are also larger, but only one or two are present in a lung field; they are rarely seen in this condition.) At this stage of fibrosis, there is definite limitation of motion of the diaphragm, more marked on expiration than on inspiration. Paradoxical motion of the mediastinum, heart, and trachea is generally noted. In a few cases there is widening of the trachea, as Hampton (4) has pointed out, and this sign, when present, is of considerable significance in making the diagnosis (Fig. 4).

There is a form of idiopathic pulmonary fibrosis and emphysema in which the emphysema is greatly out of proportion to the fibrosis (Fig. 5). The fibrous strands are much smaller, are not systematically arranged, and are located chiefly between blebs and bullae, or about large pneumatoceles. The clinical picture is similar to that when fibrosis predominates.

In many instances, the heart shadow may be poorly delineated because of numerous areas of fibrosis, which may obliterate the margins of the cardiac silhouette; in others, it may be possible to determine right ventricular enlargement (Fig. 6). Cor pulmonale, however, is undoubtedly present far oftener than is apparent from the roentgen evidence alone. Careful correlation of the clinical and roentgenologic findings should make possible more accurate diagnosis.

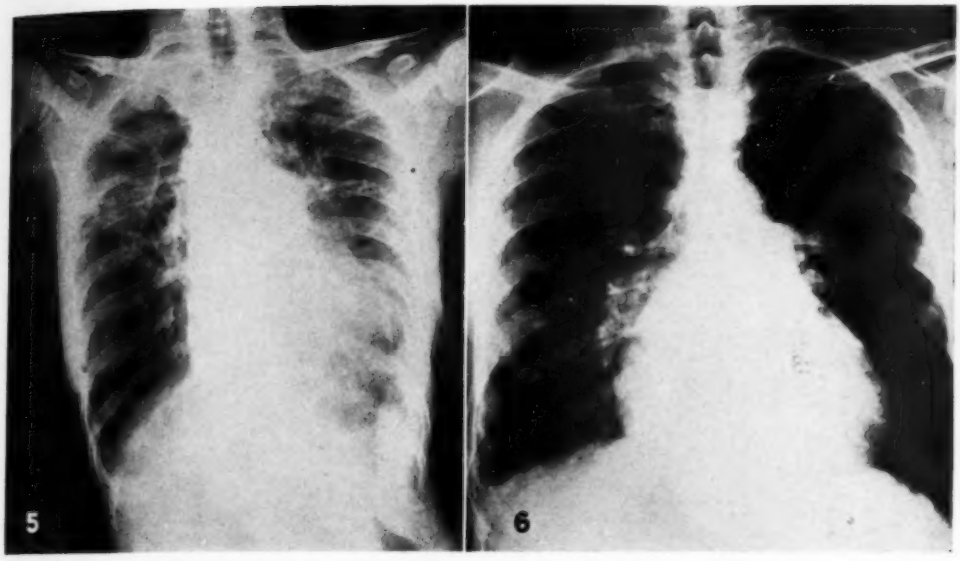

Fig. 5. Pulmonary fibrosis with emphysema predominating. Note that the fibrosis is not diffuse. The emphysema in the inferior part of the right lung is marked; there are considerable flattening of the diaphragm and cardiac enlargement (old mitral lesion).

Clinical: The patient, a woman of 53, had a mild upper respiratory infection for one week before admission. She had been dyspneic, with a hacking cough and fever of 100°, for two days. On the day of entry she was found pulseless and in shock and was brought to the hospital in that condition. There was no history of hay fever or of asthma. Death occurred twenty-four hours after admission.

Autopsy: Marked pulmonary emphysema; some fibrosis was noted microscopically. There was no evidence of tuberculosis.

Fig. 6. Cor pulmonale in emphysema due to asthma (grid film). The cardiac enlargement is much more apparent than in cases of the usual type of fibrosis and emphysema. Note the prominent pulmonary artery shadows. The large chest and emphysematous lungs are quite apparent, as well as the low diaphragm, which fluoroscopically showed limited motion.

Clinical: The patient, a man of 40, had suffered from asthma most of his life. For two months before admission there had been swelling and tenderness in the right upper quadrant, and for one month, severe dyspnea on exertion.

Autopsy: Marked emphysema and cor pulmonale, with the right ventricle measuring 10.0 mm. and the left, 16.0 mm.

DIFFERENTIAL DIAGNOSIS

Radiation fibrosis is usually localized to the areas of treatment. It is, presumable, however, that x-radiation and/or gamma-radiation could produce a fibrotic process that might be indistinguishable from idiopathic pulmonary fibrosis.

In the early stages of *asthma* there may be no characteristic roentgen findings except during an attack, when fluoroscopy will demonstrate limitation of expiratory motion of the diaphragm. As the emphysema secondary to the asthma becomes more severe, the brightness of the lung fields, as well as wide spaces between the markings, is more apparent, and in many instances blebs and bullae develop, with intervening areas of fibrosis (Fig. 7). The roentgen appearance may be identical with that of the type of idiopathic fibrosis and emphysema in which the emphysema is predominant (Fig. 8).

The roentgen appearance of the primary phase of *pneumoconiosis* is much like that of the early stage of idiopathic pulmonary fibrosis. Both present a diffuse increase in the strand-like shadows throughout the lung fields lying in close approximation to the vascular structures; often there is a certain amount of nodularity. As the silicotic process begins to show coalescence, there is generally more emphysema at the apices than is found in the so-called idiopathic cases, with large confluent areas of density in the mid-lung fields.

Raynaud's disease, scleroderma, and peri-

Fig. 7. Emphysema and fibrosis secondary to asthma. Numerous large emphysematous blebs are present, particularly in the upper lung fields. The fibrosis is most apparent in the mid-portion of the right lung. Fluoroscopically, the motion of the diaphragm was limited.

Clinical: The patient, a man of 35, gave a history of asthma since the age of seven; he had been unable to work for ten years before admission. He entered the hospital during an acute asthmatic attack and showed the progressive changes of cardiac failure until death.

Autopsy: Cor pulmonale; also evidence of old rheumatic heart disease involving aortic, mitral, and tricuspid valves. Bilateral fibrosis and emphysema.

arteritis nodosa frequently produce a diffuse type of fibrosis, often more marked in the lower lung fields than in the apices.

Miliary tuberculosis presents an appearance which at times may be confused with fibrosis, but the history and the general clinical condition of the patient will usually aid in the differential diagnosis.

Sarcoid and erythema nodosum with pulmonary changes are roentgenologically very like the conditions previously noted. They are distinguished, as a rule, by symmetrical enlargement of the hilar and mediastinal lymph nodes. Variations may be seen, however, in which the node enlargement is pronounced while the pulmonary changes are minimal or absent, or in which the pulmonary abnormalities are present and the hilar and mediastinal nodes

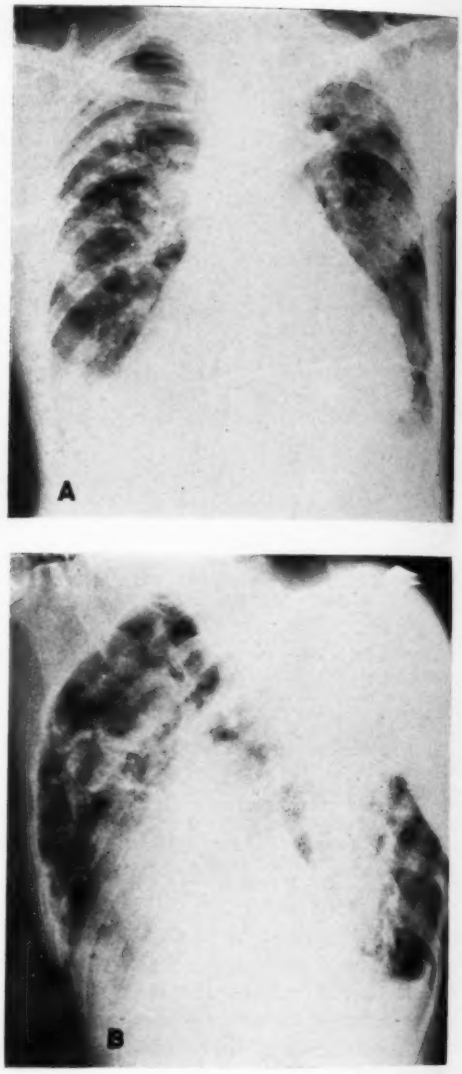

Fig. 8. Fibrosis and emphysema secondary to asthma. The appearance is similar to that of patients with markedly advanced idiopathic pulmonary fibrosis and emphysema (Figs. 3 and 4 B). The heart is considerably enlarged.

Clinical: The patient, a woman of 51, had suffered from asthma for thirty-eight years. On admission the characteristic findings of cor pulmonale with failure were evident.

Autopsy: Marked pulmonary emphysema and fibrosis; cor pulmonale.

are within the limits of normal (Fig. 10).

A somewhat similar appearance has been noted recently among certain people who have been exposed to *beryllium*. The exact

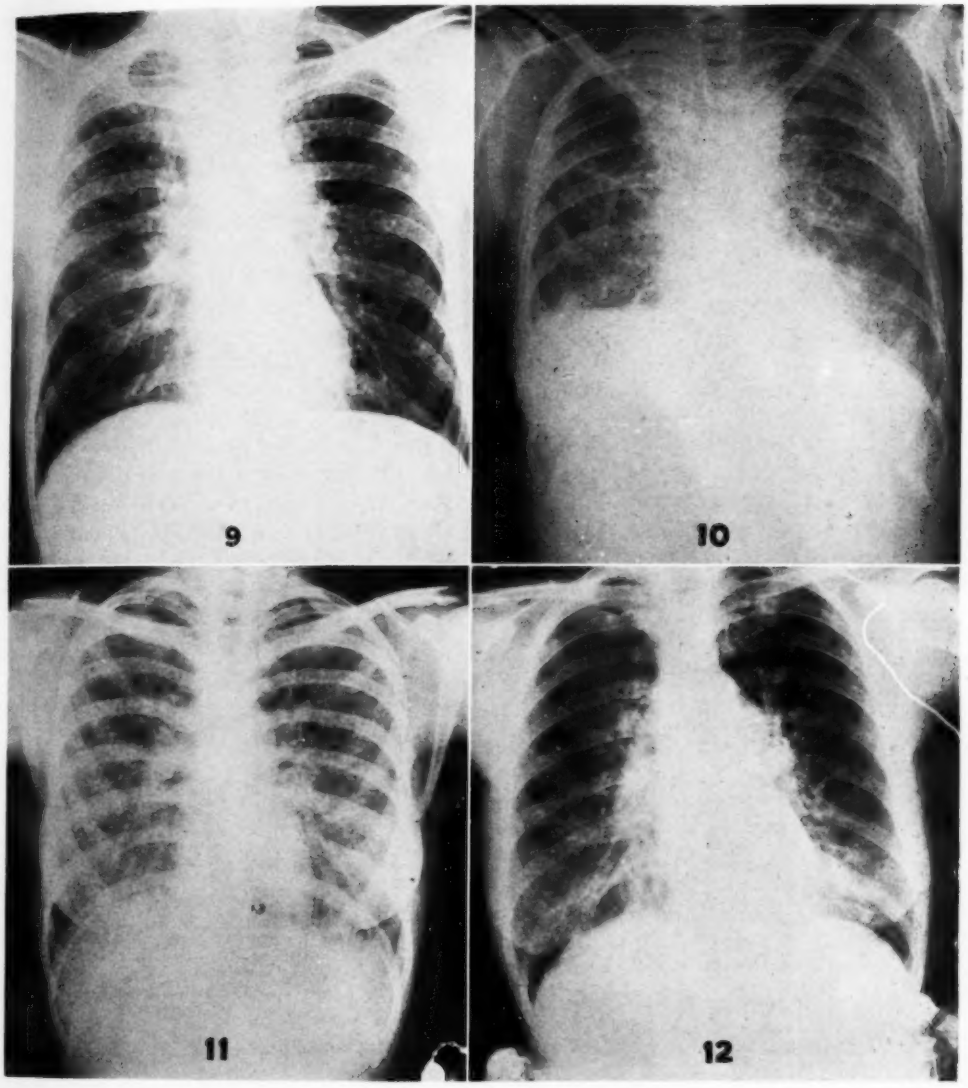

Fig. 9. Pneumoconiosis. The slight prominence of the markings throughout the lung fields is not unlike that of the early stages of idiopathic pulmonary fibrosis.

Clinical: The patient, a man of 40, had been a granite worker between the ages of eighteen and thirty years.

Fig. 10. Atypical sarcoid, simulating pulmonary fibrosis. A diffuse process, both linear and nodular, is evident throughout the lung fields. The widened superior mediastinum presents a less lobulated outline than is usual in sarcoid, and there is some pleural fluid on the right.

Skin Biopsy: Sarcoid.

Fig. 11. Beryllium exposure. There is a fine nodularity throughout the lung fields with some increase in the linear strands and rather marked prominence of the hilar shadows.

Clinical: The patient, a woman of 23 years, had been exposed in mild degree to beryllium for four years. The clinical picture was similar to that of others who have experienced the same exposure.

Fig. 12. Lymphatic spread of metastases from carcinoma of rectum. The slight prominence of the linear shadows is similar to that seen in the early stages of pulmonary fibrosis. There is somewhat greater enlargement of the hilar lymph nodes, however.

nature of this condition is not completely understood at the present time, although the question has been raised as to whether it is a sarcoid-like type of disease. Clini-

cally the two are different; patients who have been exposed to beryllium tend to experience many more symptoms of emphysema and of general discomfort than do those suffering from sarcoid (Fig. 11).

Degenerative vascular lesions involving extensive areas of the pulmonary arteries and arterioles may likewise simulate a diffuse fibrotic process. Long-standing cardiac decompensation can produce a similar roentgenologic appearance, as may propagating pulmonary thromboses, but in the latter a diminution in the pulsations of the pulmonary arteries is apparent fluoroscopically.

Lymphatic spread of carcinomatous metastases (7) roentgenologically is very like the early stages of idiopathic pulmonary fibrosis. There is a diffuse increase in the markings throughout the lung fields. It may be noted, however, that many of these linear shadows extend to the periphery of the lung and become slightly wider at the pleural margin, and hilar node enlargement is often evident. With lymphatic spread, the diaphragm as a rule shows fairly good respiratory motion, and blebs are not demonstrable; the patient complains of progressively severe dyspnea over a relatively short period of time (Fig. 12).

Changes in the lungs associated with *pancreatic achylia* and with *Letterer-Siwe's disease* may simulate the roentgen appearance of pulmonary fibrosis.

It must be emphasized that enlargement of pulmonary blood vessels and lymphatic channels may have the same roentgenologic appearance as pulmonary fibrosis, whatever its etiology, before emphysema becomes evident. This is due to the fact that anatomically these vessels, as well as the bronchi, are located in the area where fibrosis may first appear. Present knowledge indicates that accurate differential diagnosis may be impossible. Indeed, it seems not unlikely, after reviewing the known causes of fibrosis, that any distinct entity without an etiologic factor exists, but rather that other, as yet unrecognized, causes must still be sought.

CONCLUSIONS

1. Roentgenologically, idiopathic pulmonary fibrosis is, as a rule, a diffuse process.

2. In its early phase, idiopathic pulmonary fibrosis may not be distinguishable from numerous other processes.

3. In the later stages, the most common roentgen appearance is that of a generalized process with more or less systematically arranged areas of fibrosis interspersed with areas of emphysema.

4. Careful technic in the roentgen examination, including determination of the position and motion of the diaphragm, is necessary to the making of a correct diagnosis.

5. The fundamental requirement for accurate diagnosis is the correlation of clinical, pathologic, and roentgenologic findings.

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SUMARIO

Fibrosis Pulmonar Idiopática: Hallazgos Radiológicos

El aspecto roentgenológico de la fibrosis pulmonar idiopática se parece algo al de la fibrosis debida a varias causas conocidas, y sólo puede hacerse el diagnóstico después de correlacionar los hallazgos clínicos y radiológicos con la patología conocida de otros casos.

Al principio de la evolución de la dolencia, la única anomalía discernible tal vez sea un ligero relieve de las demarcaciones en todos los campos pulmonares. Rara vez se observan algunas flictenas o zonas localizadas de enfisema. Si el estado se halla moderadamente avanzado, nótase nuevo aumento de las sombras lineales, con cierta tendencia a nodulación. Suele afectarse la movilidad del diafragma y las zonas enfisematosas son más pronunciadas. En las últimas etapas, el cuadro más común es el de un proceso generalizado con zonas de fibrosis ordenadas más o menos sistemáticamente e intercaladas con zonas de enfisema. Existe una limitación bien definida de los movimientos del diafragma, sobre todo en la expiración. Nótase generalmente un movimiento paradójico del mediastino, el corazón y la tráquea. Hay a veces dilatación de la tráquea, lo cual reviste considerable importancia diacrítica.

En el diagnóstico diferencial hay que considerar los siguientes estados: asma, neumoconiosis; enfermedad de Raynaud, escleroderma y periarteritis nudosa; granulia; sarcoide y eritema nudoso; envenenamiento por berilio; lesiones vasculares degenerativas; difusión linfática de metástasis carcinomatosas; y patología pulmonar asociada a aquilia pancreática y enfermedad de Letterer-Siwe.

En el examen roentgenológico una técnica esmerada es indispensable. Los puntos de mayor valor son: la roentgenoscopia, dedicando en particular atención a la posición y movilidad del diafragma, una radiografía postero-anterior, y una vista lateral o ambas proyecciones oblicuas.

Pathology of Pulmonary Fibrosis, Including Chronic Pulmonary Sarcoidosis[1]

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PROLIFERATION of fibroblasts resulting in the development of abnormal fibrous tissue in the lung is a common sequel of many types of injury to the pulmonary parenchyma. In fact, few lungs of adult individuals are found free from foci of fibrosis postmortem. The term "pulmonary fibrosis," however, is rarely used as a diagnosis when the etiology of the fibrous reaction is obvious, as in fibroid phthisis, lipoid pneumonia, or silicosis, nor is it commonly applied to localized scars such as healed infarcts, but is reserved for examples of multifocal or generalized involvement of the lungs, the origin of which is dubious or unknown. It is the pathology of this latter group which is the subject of the present paper.

Upon review of a series of 6,000 postmortem examinations performed in the pathology laboratory of the Massachusetts General Hospital, it was found that an anatomic diagnosis of pulmonary fibrosis corresponding to the limited definition given above had been made on only 59 occasions. In 36 the lesion was considered an incidental autopsy finding and was not regarded as having contributed either to the patients' symptoms during life or to their demise. In only 23 was it sufficiently extensive or severe to have probably been of clinical significance. Pulmonary fibrosis is, therefore, an uncommon disease, in contrast to pulmonary emphysema, for example, which was recorded in approximately 10 per cent of the same series of autopsy protocols.

In the following discussion the pathogenesis of pulmonary fibrosis will be reviewed, its consequences briefly mentioned, and the incidence of various types compared. Finally, three types which are of particular interest will be considered in detail.

PATHOGENESIS OF PULMONARY FIBROSIS

Fibroblastic proliferation in the lung develops in response to the same stimuli as in other tissues, but the anatomic structure of the lung produces certain characteristic patterns. Four chief types may be recognized, which may be found singly or in any combination.

(1) *Organization of Intra-alveolar Fibrinous Exudates:* Fibrous tissue may develop in large amounts within the smaller air passages and the alveoli as the result of organization of fibrin produced in the course of bronchitis or pneumonic exudation which has failed to undergo resolution. This mechanism may result in the relatively uncommon bronchiolitis obliterans and the more frequent organizing pneumonias. Such lesions may be localized in a single lobe or scattered in many foci throughout any or all lobes.

The fibrotic patches resulting from organized pneumonia are usually readily recognizable in sections stained for elastic tissue, which brings out clearly the pattern of the shrunken, lumenless alveoli in areas which seem diffusely collagenous with hematoxylin and eosin (Fig. 1).

An interesting relationship of this type of fibrosis to bronchial asthma will be discussed below.

(2) *Healed Infarction:* Infarction of the lung, if uncomplicated by infection, never produces total destruction of the parenchyma, and the elastic fibrils in particular survive to condense, with shrinkage of the lesion, into whorled and matted masses like tangles of coarse black hair, which Castleman (1) showed were diagnos-

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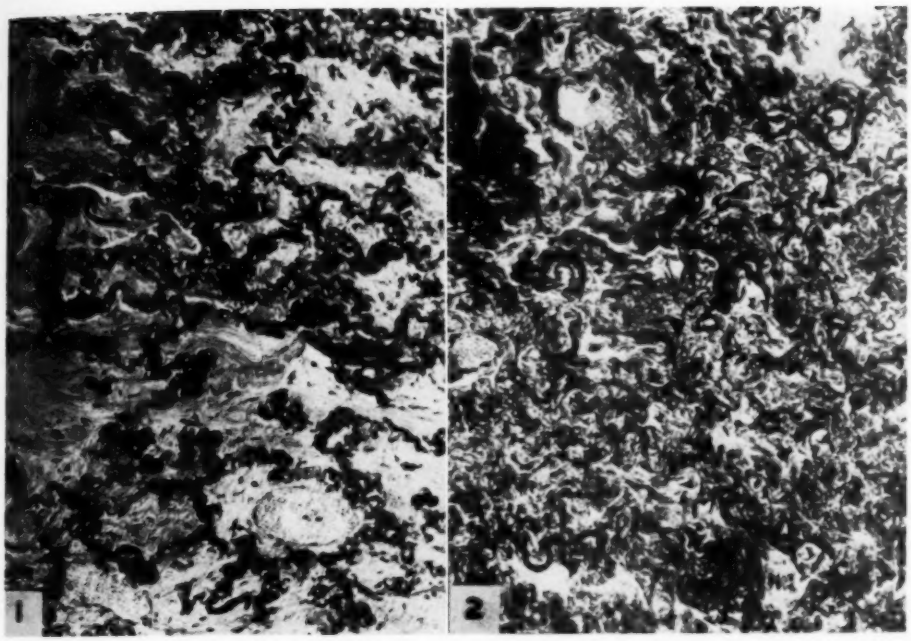

Fig. 1 Organized pneumonia. The elastic-tissue stain brings out clearly the pattern of the obliterated alveoli. × 50

Fig. 2. Healed infarction. The persistent elastic fibrils have condensed into whorled and matted black tangles. × 50

tic of healed infarction (Fig. 2). Though multiple foci of healed infarction due to embolism are theoretically a possible cause of diffuse pulmonary fibrosis, it is improbable that many patients survive the acute stage of the disease. Only one case in the present series was attributable to this mechanism, and the lesion was only an incidental autopsy finding. It might be supposed that the more slowly developing vascular occlusion of idiopathic pulmonary arteriosclerosis (Ayerza's disease) would be more likely to produce widespread injury to the pulmonary parenchyma; yet in only 1 of 6 cases were significant patches of fibrosis noted.

(3) *Healed Destructive Pneumonitis:* Fibrosis is the inevitable final result of healing of any focus of necrotizing infection in the pulmonary tissue. Two types of infections are particularly prone to produce necrosis in the lung, the infectious granulomata, with tuberculosis far in the lead, and septic mixed infections, which are usually associated with abscess formation or bronchiectasis. With the advent of modern chemotherapeutic and antibiotic therapy, we may expect to see more healed lesions attributable to such antecedents. In distinguishing organized pneumonia or healed infarction from the scars of necrotizing infections, the elastic-tissue stain is once again our mainstay, since elastic fibrils are destroyed in the latter group.

(4) *Interstitial Fibrosis:* Interstitial fibrosis may develop predominantly in the alveolar walls or may be concentrated in and about the lymphatic channels. In the latter instance, the pattern is distinctive, since the lymphatics run in the peribronchial and perivascular tissues, in the interlobular septa, and beneath the pleura. Commonly, however, both areas are simultaneously involved.

The commonest source of alveolar wall fibrosis is prolonged passive congestion of the lung, usually from valvular heart disease. It is usually, however, slight in de-

gree and constitutes such a minor element in the general picture of cardiac failure that it is rarely thought of when the term "pulmonary fibrosis" is used. Only three times in our series of 6,000 necropsies did we record alveolar wall fibrosis in our list of anatomic diagnoses, and in each of these cases there was severe pulmonary arteriosclerosis.

Interstitial pneumonia might be expected on occasion to produce alveolar wall fibrosis, and rheumatic pneumonitis, sulfonamide injuries, virus and rickettsial infections are possible causes of this type of lesion, but proof of such etiologic backgrounds has yet to be supplied. Hamman and Rich (2) have recently described a severe form of injury to alveolar walls with consequent fibrosis but were unable to identify the etiologic factor.

A relatively pure form of alveolar wall fibrosis is seen in patients who have had excessive irradiation of the lungs, usually for malignant disease. However, more complicated pictures are frequently seen, and discussion of this problem will be reserved for a later paragraph.

Lipoid pneumonia is a significant cause of interstitial fibrosis. In the early stages of the disease, the fat within the alveolar lumina is rapidly phagocyted, and little, if any, fibroblastic proliferation occurs within the alveoli. Much of it is rapidly transported into the alveolar walls where reticular fibrils quickly develop about the phagocytes. As the latter degenerate, the reticulum condenses into dense collagenous tissue. In the later stages, it is frequently impossible to distinguish whether the fibrous tissue has arisen within the alveolar lumina or in the interstitial tissues.

Silica is the agent which most characteristically produces extensive fibrosis in and about the pulmonary lymphatics, to which it is rapidly transported by mobile phagocytes. Considerable alveolar wall fibrosis always develops as well.

A final type of interstitial fibrosis, which may produce very extensive destruction of pulmonary parenchyma, is the result of a granulomatous process characterized by miliary, non-caseating tubercles which develop in the alveolar walls. By fusion of individual lesions, large areas of parenchyma become involved. A detailed discussion of this lesion and its relation to sarcoidosis will be presented below.

PATHOGENETIC TYPE AND ETIOLOGY

It should be emphasized that the classification of pulmonary fibrosis which has been outlined above is based upon pathogenesis, not upon etiology. Tubercle bacilli, for instance, may cause exudative pneumonia which heals by organization, as in the usual subpleural apical scar, or extensive necrosis of parenchyma when caseation occurs. Moreover, more than one type of fibrosis is frequently present in the same case.

CONSEQUENCES OF PULMONARY FIBROSIS

Widespread fibrosis of the lung interferes with normal pulmonary function in several ways. The increase in collagen is frequently coupled with distortion and even frank destruction of elastic tissue, which must diminish the elasticity of the organ and decrease the efficiency of ventilation. When alveoli are obliterated, ventilating surface is diminished and fibrotic alveolar walls usually show decreased vascularity. Frequently the loss of local respiratory function is evidenced by the development of an alveolar lining of cuboidal "metaplastic" epithelium.

Permanent collapse or destruction of alveolar tissue leads, as Loeschke (3) showed, to disproportion between thoracic and pulmonary volumes and hence to emphysema, bronchiectasis, or a combination of the two conditions. Finally, the decrease of the vascular bed and the inefficient pulmonary ventilation frequently are followed by pulmonary hypertension and cor pulmonale. Pulmonary fibrosis, therefore, may produce either the symptoms of pulmonary insufficiency or of right-sided heart failure. The reserve factor, however, is so great that the lesion must be very severe before symptoms of either type occur.

FREQUENCY OF PATHOGENETIC TYPES OF PULMONARY FIBROSIS

The relative frequency of these various types of pulmonary fibrosis and their etiologic backgrounds is shown in Table I. The pair of columns on the left covers total incidence, those on the right the cases of sufficient severity to have been judged clinically significant.

TABLE I: TYPES OF PULMONARY FIBROSIS (59 CASES)

Type	Total Number	Clinically Significant
1. *Organized pneumonia*	*19*	*8*
Bronchial asthma	10	6
2. *Healed infarction*	*1*	
3. *Healed necrotizing pneumonitis*	*23*	*7*
Bronchiectasis	9	2
Lung abscess	2	
"Radiation pneumonitis"	6	4
Type uncertain	6	1
4. *Interstitial fibrosis*	*16*	*6*
Rheumatic heart disease	3	
Ayerza's disease	1	
Radiation pneumonitis	6	
Sarcoidosis	6	6

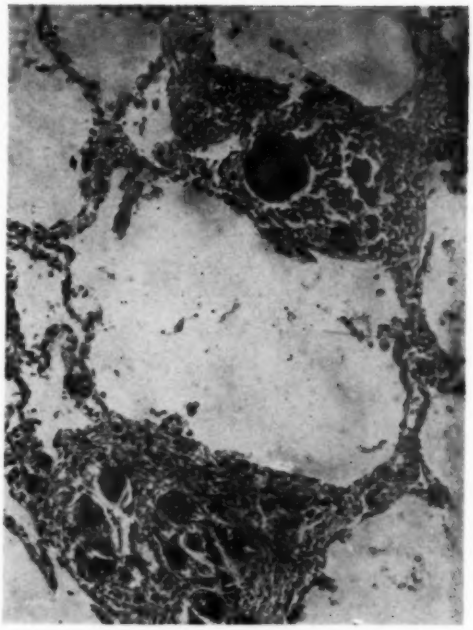

Fig. 3. Miliary epithelioid tubercles with giant cells but without caseation, characteristic of sarcoid developing in the wall of an alveolus. × 100

It is apparent from inspection of the table that three groups of patients are particularly likely to develop significant grades of pulmonary fibrosis. These are victims of bronchial asthma, patients who have received x-radiation over the chest, and those with sarcoid-like lesions. Each of these groups is sufficiently numerous and of enough importance to deserve closer examination.

ORGANIZED PNEUMONIA IN BRONCHIAL ASTHMA

Organized pneumonia, or rarely bronchiolitis, accounted for 19 cases of pulmonary fibrosis, and 8 of these were judged clinically significant. It is of considerable interest that 10 of the group, including 6 of the clinically significant cases, appeared in patients with chronic bronchial asthma. Since there were only 60 asthmatics in the entire 6,000 autopsies, the 10 per cent incidence of organized pneumonia is too high to be coincidental. By what mechanism bronchial asthma delays the resolution of pneumonic processes, and therefore favors organization, is quite unknown. It may be purely mechanical in impeding drainage of the affected alveoli; it may be a by-product of the allergic status of these patients. In any event, bronchial asthma must be considered a significant factor in the production of pulmonary fibrosis.

RADIATION PNEUMONITIS

It would be profitless to attempt a detailed description of radiation pneumonitis on this occasion, since it has been authoritatively described by Warren (4) and his collaborators. In relation to our pathogenetic classification of fibrosis, however, it is interesting to note that half of the cases fall in the alveolar wall fibrosis group and half in the necrotizing pneumonitis. The former probably represent the comparatively pure effect of radiation injury, the latter present complex pictures built up of direct radiation effect, superimposed infectious pneumonitis, foci of infarction due to vascular injury, and even scars of healed neoplastic disease. In cases of Hodgkin's

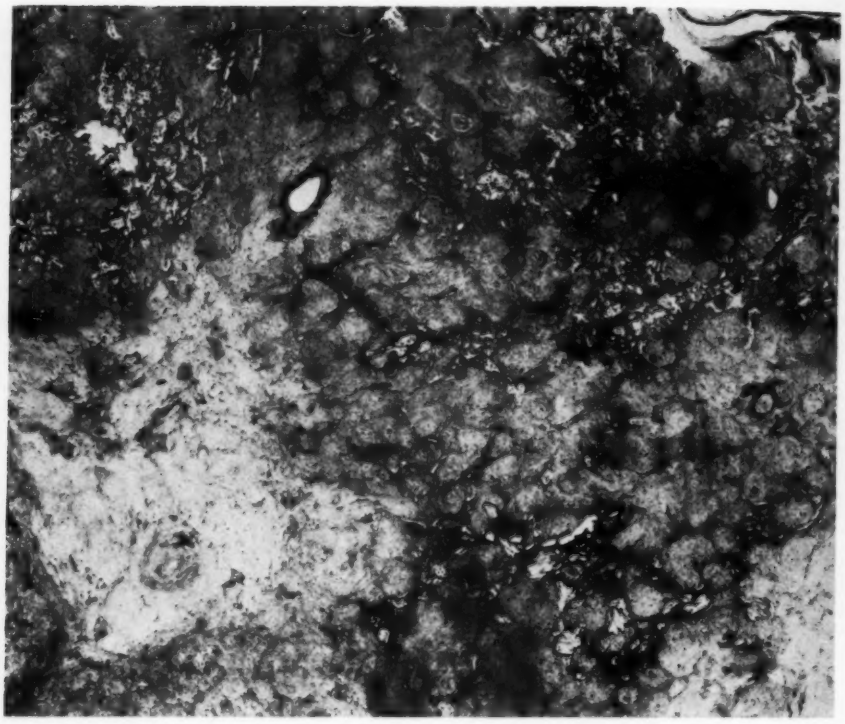

Fig. 4. All stages of confluence of miliary lesions into homogeneous, patternless, almost acellular fibrous tissue such as surrounds the obliterated blood vessel in the lower, left corner. In the lower right corner a few circular clefts are just visible at this magnification. × 20

disease it is particularly difficult, and often impossible, to identify the latter.

GRANULOMATOUS PNEUMONITIS

This group of 6 cases is of particular interest, since all of them were clinically significant and in all the degree of fibrosis was severe. They are all alike in that extensive and obviously long-standing fibrosis was accompanied by acute progressive lesions of a miliary granulomatous type (Fig. 3). The latter consist of tubercle-like collections of epithelioid cells and giant cells without central caseation or other form of necrosis. They are frequently bordered by a narrow zone of lymphocytes, and in other instances are encapsulated by fibroblasts. In the older lesions the fibroblasts become more numerous, and eventually the epithelioid tubercle is completely replaced by almost acellular whorled collagen.

The tuberculoid lesions appear always to develop in the interstitial tissues, never in the lumina of alveoli or air passages. The oldest lesions are found beneath the pleura and about the blood vessels and bronchi, especially near the hilus. Spreading out from these areas, fresher tuberculoid lesions are found in the alveolar walls, which become grossly thickened and distorted. Contiguous lesions eventually fuse, and all traces of normal lung architecture are lost over large areas ranging from a few millimeters to three or four centimeters in diameter (Fig. 4). The process invades the walls of the bronchi, completely destroying the cartilages (Fig. 5). Blood vessels are somewhat more resistant, but they, too, are invaded, thrombosed, and portions of the musculoelastic media may be cleanly destroyed (Fig. 6). The large scars resulting from the confluence of miliary lesions are densely

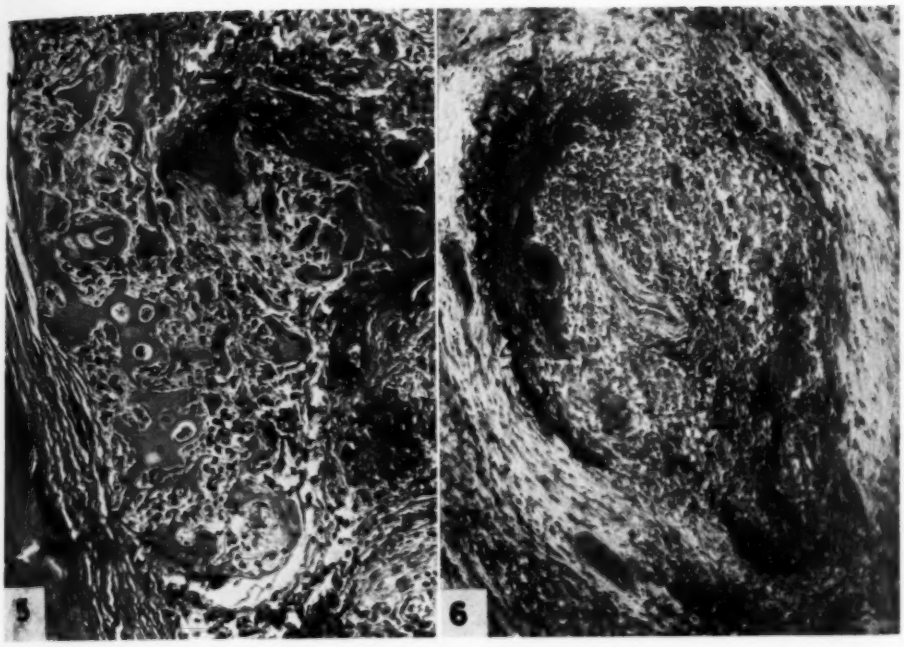

Fig. 5. Invasion and partial destruction of a bronchial cartilage by the granulomatous process. × 50
Fig. 6. Invasion of a pulmonary artery with focal destruction of the musculo-elastic medial layer and thrombosis of the lumen. A single canalizing vessel is present. × 50

collagenous, with a very small cellular content. Foci of necrosis may develop but never caseate or calcify. Scattered anthracotic particles are frequently numerous, but dense anthracosis is unusual. Many scars contain acicular clefts and these are frequently arranged in sheafs with parallel or slightly radiating long axes. They may or may not be surrounded by giant cells. With the elastic-tissue stain no trace of alveolar walls can be made out, but irregular dense masses of elastica persist in focal areas. Many, though not all of these, can be identified as the remnants of obliterated blood vessels. Usually no trace of bronchial structures can be recognized in the older and larger scars. In the persisting alveolar tissue severe bronchiolectasis and emphysema frequently develop (Fig. 7).

The severity of the fibrotic process was always obvious on gross examination. The pleura was often thick, and the pleural surfaces were irregularly distorted, deeply pitted scars alternating with emphysematous bullae. On two occasions the prosector described the lung as multilobular and compared it in appearance to a hepar lobatum. On section, the tissue cut with greatly increased resistance and the cut surfaces revealed small and large foci of dense, grayish, patternless or slightly whorled fibrous tissue. The usual gross diagnosis at the autopsy table was silicosis, and it seems doubtful if the two lesions can be grossly distinguished.

Coarse emphysema was present between the fibrous scars in all cases, the bullae ranging up to 10 mm. in diameter. In 3 cases there was also bronchiolectasis. Cor pulmonale of significant grade was present in 4 of the 6 cases, the right ventricles measuring from 6 to 8 mm. in thickness.

The etiology of the process remains uncertain. The lack of caseation and of calcification makes tuberculosis unlikely. In all cases, Ziehl-Neelsen stains of the tissues have failed to show organisms. Careful search for mycoses has shown nothing, and none of the patients, so far as

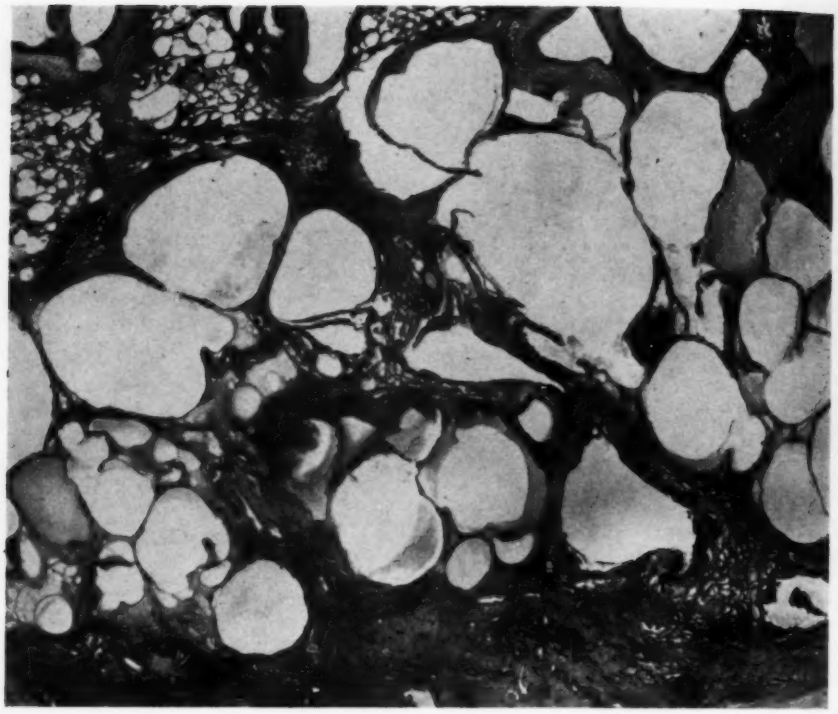

Fig. 7. Development of severe bronchiolectasis and emphysema adjacent to large area of pulmonary fibrosis, the edge of which is included at the lower margin of the picture. × 20

known, had ever been in an endemic area for coccidioidal infection.

The older scars are indistinguishable, with ordinary staining methods, from silicosis, but contain only rare and scattered crystals when viewed with polarized light. Though none of the patients had any history of exposure to silicious dust, material from two cases was examined chemically for silica. The values were not above those of control lungs. Though specific enquiries were not made, it is believed very improbable, in view of the patients' occupations and, in the earlier cases, the date of death, that there was any exposure to beryllium.

The clinical data are of little help. None of the patients gave a history of any acute respiratory infection and only one, suffering from a terminal subacute bacterial endocarditis, was observed to be febrile. Sputum was obtained in 4 cases, and all specimens were negative for acid-fast bacilli on smear; in 3 instances guinea-pig inoculations were likewise negative. The diagnosis of sarcoid was considered during life in only one of these patients. Her tuberculin test was negative at 1 to 1,000 and was not repeated in lower dilutions. No tuberculin tests are recorded in the other case histories. No patient had uveitis, parotitis, dactylitis, splenomegaly, generalized lymphadenopathy, or cutaneous lesions.

Postmortem examination offered almost equally little evidence of generalized sarcoidosis. The hilar nodes were enlarged and densely fibrotic in all cases. Occasionally an incompletely sclerosed epithelioid tubercle could still be found. In one case a retroperitoneal node (Fig. 8) and in another the spleen (Fig. 9) showed miliary lesions entirely consistent with sarcoid.

The criteria of diagnosis of sarcoid are

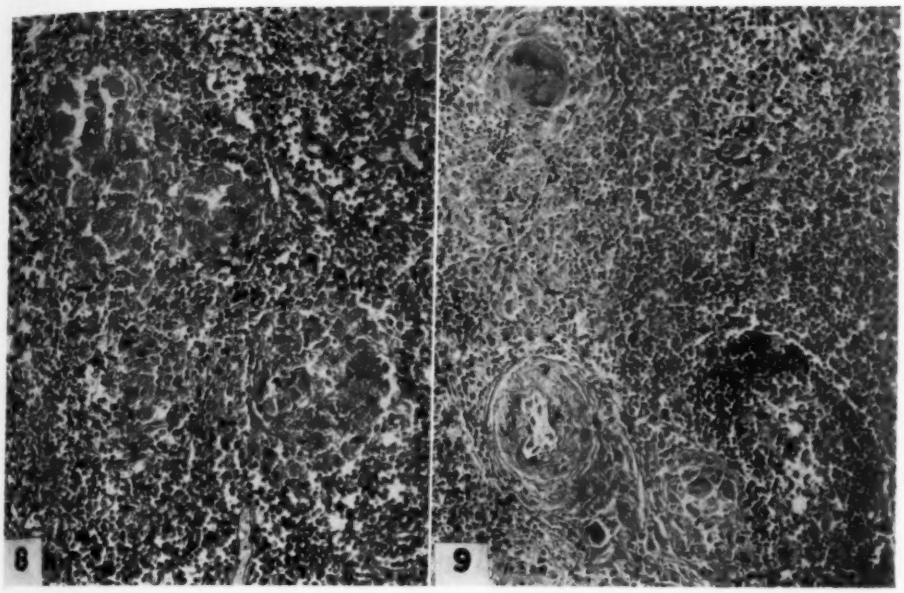

Fig. 8. Two miliary collections of epithelioid cells, consistent with sarcoidosis, from a retroperitoneal lymph node in one of the cases of severe pulmonary fibrosis. × 200

Fig. 9. Two miliary granulomata, consistent with sarcoidosis, the upper one with a large giant cell, from the spleen of another case of pulmonary fibrosis. × 150

still unsatisfactory. The histologic lesion cannot be considered specific, as recent experience with beryllium toxicity has re-emphasized, and the characteristic pattern of systemic involvement is still necessary for certain diagnosis. The pulmonary lesion described in these 6 cases is consistent with changes in the lung which have been described in patients with characteristic generalized sarcoidosis (5, 6). It seems probable that these cases fit within the pathologic complex termed "sarcoidosis" and that our concept of the disease must be enlarged to include predominant or exclusive localization in the lungs with progressive pulmonary fibrosis leading to death from pulmonary insufficiency.

SUMMARY

The pathogenesis of pulmonary fibrosis has been reviewed. Four types are described: (1) organized pneumonia, (2) healed infarction, (3) healed necrotizing pneumonitis, and (4) interstitial fibrosis. In a survey of 6,000 necropsies, 59 cases of pulmonary fibrosis (exclusive of tuberculosis, silicosis, and lipoid pneumonia) were recorded. Of these, 23 were judged to be clinically significant. Among this number, three groups were considered of sufficient interest to warrant special discussion. In the latter it is pointed out that the incidence of organized pneumonia in patients with chronic bronchial asthma is too high to be coincidence, that in radiation pneumonitis the picture is frequently complicated by the scars of necrotizing pneumonitis and of healed neoplasia. Finally, a progressive form of granulomatous pneumonitis healing by fibrosis has been described, and the evidence for considering this a form of localized pulmonary sarcoidosis has been presented.

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SUMARIO

Patología de la Fibrosis Pulmonar, Comprendiendo Sarcoidosis Pulmonar Crónica

En un repaso de 6,000 autopsias ejecutadas en el laboratorio de anatomía patológica del Hospital General de Massachusetts, se anotaron 59 casos de fibrosis pulmonar (exclusive de tuberculosis, silicosis y neumonía lipoidea). Desde el punto de vista de la patogenia, las mismas correspondían a cuatro formas: neumonía organizada, infarto cicatrizado, neumonitis necrosada cicatrizada y fibrosis intersticial.

En 36 de los casos, la fibrosis constituyó un hallazgo incidental de la autopsia y no se consideró que hubiese contribuído a los síntomas durante la vida o a la muerte. Treinta y tres casos se consideraron de significación clínica. Entre ellos, tres grupos poseían suficiente interés para justificar una discussión especial. Los puntos resaltados en particular fueron los siguientes: (1) La incidencia de neumonía organizada en los enfermos con asma bronquial crónica es demasiado alta para que sea mera coincidencia. (2) En la neumonitis irradiatoria el cuadro se ve frecuentemente complicado por cicatrices de neumonitis necrosada y de neoplasia curada. (3) Existe una forma evolutiva de neumonitis granulomatosa que cura por fibrosis y presenta características compatibles con las alteraciones pulmonares descritas en los enfermos con sarcoidosis generalizada. Considérase probable que los casos de este último tipo representen una forma de sarcoidosis pulmonar localizada.

Pulmonary Fibrosis: Clinical Aspects[1]

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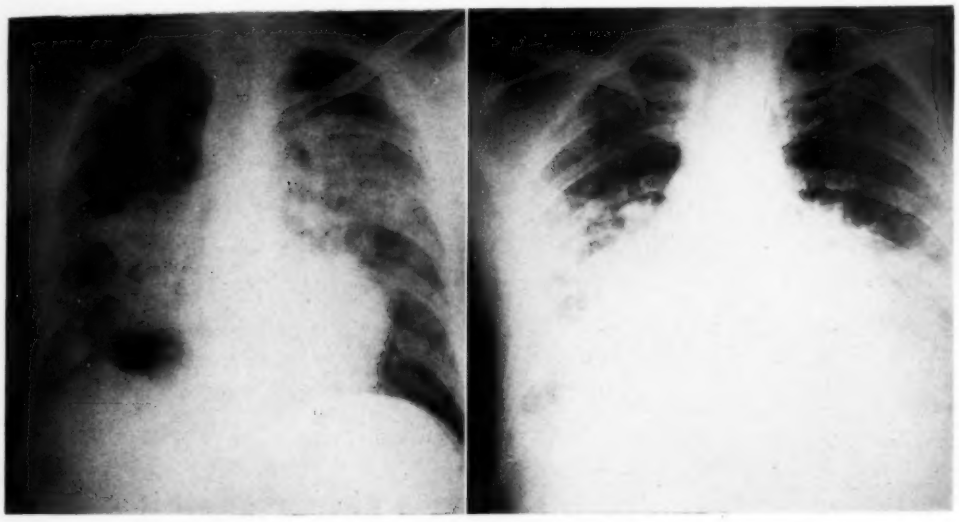
MY CONTRIBUTION to this symposium on pulmonary fibrosis will be short, since my only object is to try to correlate the x-ray, pathological, and clinical findings. I believe that Dr. Mallory[2] has made a distinct contribution to our knowledge of pulmonary fibrosis and when we accept his group of cases it changes our previous ideas of classification.



Figs. 1 and 2. Fibrosing granuloma as reported by Mallory.

From the clinician's standpoint there are now four groups of cases in which varying degrees of pulmonary fibrosis play an important part: first, those with known etiology (tuberculosis, silicosis, and radiation therapy); second, the group with either asthma or emphysema, where the fibrosis seems to be the result of organizing pneumonia; third, Dr. Mallory's cases of fibrosing granulomata; and fourth, a miscellaneous group of unusual conditions.

From the standpoint of the practitioner of internal medicine, the group with "senile emphysema" is probably the largest and most important. The age of onset is usually in the fifty's. Acute respiratory infection is often the apparent inciting factor. Dyspnea with exertion is the outstanding symptom, and there are varying degrees of chronic bronchial infection and bronchial spasm. In many of these cases of emphysema, as well as in a large proportion of those with extensive fibrosis, cor pulmonale (right-sided heart failure) plays a definite part, but the severity of symptoms is often independent of the degree of pulmonary fibrosis, and cor pulmonale of alarming proportions may occur in cases with very little scar tissue. Many cases of asthma also fall into this group One of our favorite cases of clinical "idio-

[1] Presented at the Thirty-third Annual Meeting of the Radiological Society of North America, Boston, Mass., Nov. 30–Dec. 5, 1947.
[2] See preceding paper.

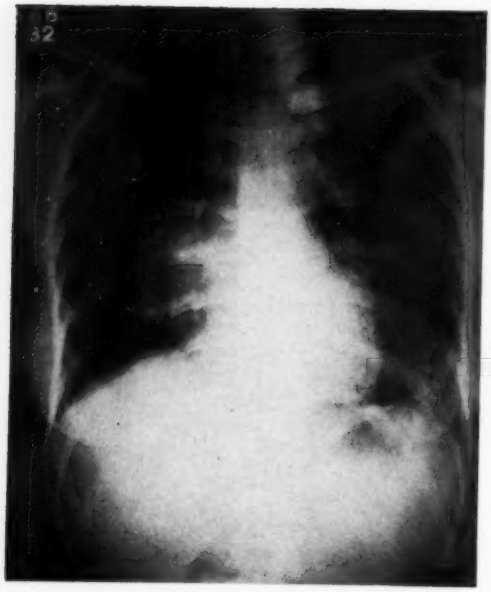


Fig. 3. Fibrosing granuloma as reported by Mallory.

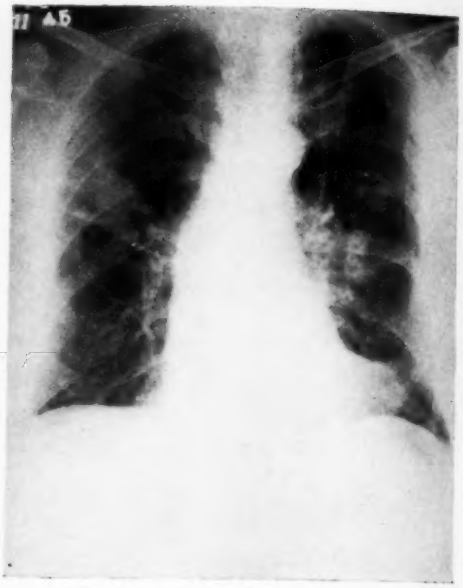


Fig. 4. Organized pneumonia in a case of emphysema.

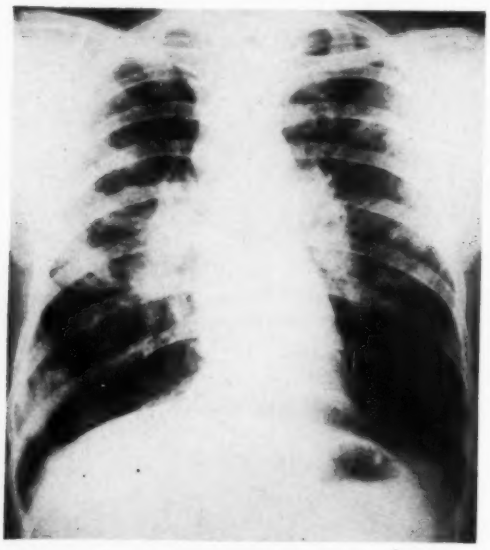


Fig. 5. "Sarcoid disease," which cleared in one year. The original diagnosis was "fibrosis."

pathic pulmonary fibrosis" was that of a woman who had had asthma since childhood; from the postmortem standpoint, this was classified as asthma with very extensive organized pneumonia. In reviewing the slides recently Dr. Mallory did not admit it to the group of fibrosing granulomata. In practically all of these cases of asthma and emphysema, such fibrosis as develops seems to be the result of organized pneumonia.

The third group is one which in the past we have called "idiopathic pulmonary fibrosis," but Dr. Mallory has shown that the majority of these cases can be placed in a group of granulomata of the lung which histologically resemble sarcoid disease. For the time being I believe that many cases in which we can safely rule out organized pneumonia should be considered as fibrosing granulomata.

This leaves for the fourth group a few miscellaneous unusual cases. We have, for example, cases resembling "fibrosis," which have proved to be bronchiolectasis, where there is a marked dilatation of the smaller bronchioles with very little dilatation or infection in the larger bronchi.

Now let us go back to Dr. Mallory's approach to the problem of "idiopathic pulmonary fibrosis" and his 6 cases of a granulomatous process, histologically similar to sarcoid disease, which have gone on to pulmonary fibrosis with resulting death.

The age of onset in all but one of the 6 was in the thirties or near-thirties. In all but one the progress was steady and relentless, with death in three to ten years. The outstanding symptom was dyspnea. Cor pulmonale occurred in 2 of the 6 cases.

Here then is a granulomatous process, histologically like sarcoid disease, which histologically is like tuberculosis (without the caseation). But clinically this condition is no more like sarcoid than sarcoid is like tuberculosis. Really to make a diagnosis of sarcoid, beside a "consistent" x-ray picture, we look for accompanying lesions of the skin, peripheral or mediastinal nodes, bones, eyes, parotid, or spleen. In only one of Dr. Mallory's cases were there granulomatous lesions outside the lungs. Moreover, we are accustomed to think of sarcoid as a benign disease which usually disappears within two years. Do we then have tuberculosis which may apparently resolve or go on to fibrosis with or without symptoms, and sarcoid disease which may resolve or go on to fatal fibrosis, and are they all forms of that most protean of all protean diseases tuberculosis?

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SUMARIO

Fibrosis Pulmonar: Fases Clínicas

Clínicamente, los casos de fibrosis pulmonar divídense en cuatro grupos: (1) los de etiología conocida (tuberculosis, silicosis, irradiación); (2) los de asma o enfisema; (3) los descritos por Mallory (en el trabajo precedente) como granulomas fibrosos; (4) un grupo vario de estados extraños. Probablemente el mayor de esos grupos es el del enfisema senil, en el cual la disnea de esfuerzo constituye el síntoma más notable y existen infección bronquial crónica y espasmo bronquial de varios grados. En muchos de estos casos el *cor pulmonale* desempeña un papel bien definido.

En el grupo de los granulomas fibrosos, previamente llamados "fibrosis pulmonar idiopática," el síntoma principal es también disnea. En los casos comunicados por Mallory, los enfermos se encontraban más o menos en la treintena, y la enfermedad iba en vías de agravación, sobreviniendo la muerte en tres a diez años. Sólo en un caso había lesiones granulomatosas extrapulmonares. Así pues, aunque el proceso histológico se parece histológicamente a la sarcoidosis, que a su vez remeda la tuberculosis, clínicamente no hay semejanza. Podemos, pues, preguntarnos, ¿existe tuberculosis que puede aparentemente resolverse o proseguir hasta la fibrosis con o sin síntomas, y sarcoidosis que puede resolverse o proseguir hasta una fibrosis letal, y son todas ellas formas de la más variable de todas las enfermedades, la tuberculosis?

Miliary Calcification of the Lung: Etiologic Aspects[1]

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EVERY RADIOLOGIST has seen numerous instances of discrete miliary calcified nodules widely distributed throughout the lung fields in patients who were apparently otherwise well. Because of the distribution of these nodules, and in the absence of proof of other etiology, they have generally been regarded as evidence of healed miliary tuberculosis. Only in recent years have epidemiologic studies demonstrated that in many patients the tuberculin reaction is negative, and where large series have been studied, the incidence of pulmonary calcification has been found to agree more closely with the number of positive histoplasmin reactors than of positive tuberculin reactors. In this communication we shall review the subject briefly and report a group of cases which we have had under observation for almost ten years, following the changing roentgen picture from the earliest evidence of disease to the stage of nodular calcification. Two cases in which there is little doubt as to a tuberculous etiology will also be included.

Blaine (2) was among the earlier writers to assume that the disseminated pulmonary calcifications occasionally demonstrated roentgenologically represented a healed miliary tuberculosis. He reported three cases, basing his conclusion as to the etiology of the lesions upon the striking resemblance of the distribution of the shadows to the appearances in acute miliary tuberculosis. None of his patients showed convincing clinical evidence of tuberculosis and in none was postmortem proof of the nature of the nodules obtained.

Sante (12), at about the same time, described a similar case, in which calcareous deposits in the lung showed little change over a period of nearly a year. While no positive evidence of tuberculosis was obtained, he concluded that the opinion of able pathologists and roentgenologists up to that time furnished "sufficient authority for a provisional diagnosis of healed miliary tuberculosis."

In a case of diffuse mottling throughout both lungs reported by Pierson (10), a lymph node biopsy suggested tuberculous involvement, but two years later the patient, without treatment or further observation, was well and the lungs had completely cleared. Two other cases of miliary calcification were attributed by Pierson to miliary tuberculosis but without clinical support.

Sutherland (15) reported a series of 38 cases of miliary calcification of the lungs and, in the absence of evidence of a tuberculous etiology, suggested the possibility of calcium metastasis, but this theory has been largely discarded.

Two cases of recovery from what was believed to be miliary tuberculosis were published in 1929 by Marlow (7). In the first case, miliary lesions in the lungs were observed for two years. Biopsy of associated cutaneous lesions led to a diagnosis of tuberculosis, but no tubercle bacilli were found in these lesions or in the sputum. The second patient had undergone nephrectomy for renal tuberculosis, and the mottling in the lung fields was considered to be of tuberculous origin. The patient refused treatment, however, and was apparently well and working one year later. In this case, also, the sputum was negative for tubercle bacilli.

Mayoral (8) reported 3 cases in 1941. One was a frank case of acute miliary tuberculosis without calcification, confirmed at autopsy. One showed miliary calcified nodules throughout the lungs, without other evidence of disease, and in

[1] From the Department of Radiology, the Henry Ford Hospital, Detroit, Mich. Presented at the Thirty third Annual Meeting of the Radiological Society of North America, Boston, Mass., Nov. 30–Dec. 5, 1947.

the third there was a history of active tuberculosis proved by laboratory and roentgenologic studies. Beginning calcification was observed in this last case twenty-seven months after the patient was first seen, and the final diagnosis was healed miliary disseminated tuberculous bronchopneumonia. In this instance a tuberculous etiology would seem to be established.

In 1943, Geever (5), a pathologist, reported a study of 2 cases in which routine chest films had shown miliary calcification, but tuberculin reactions were negative and no tubercle bacilli were found. Autopsy, following death from causes unrelated to the pulmonary lesions, revealed many small calcified nodules composed of amorphous material which, when stained, showed no tubercle bacilli and, when injected into guinea-pigs, failed to produce tuberculous lesions. In spite of this negative evidence, Geever reports the calcifications as probably tuberculous, attributing them to an infection dating back to infancy or childhood.

The possibility that a fungus infection might be responsible for miliary calcification of the lungs seems to have been first suggested by Sayers and Meriwether (13) in 1932, though these writers preferred to report their cases as due to unknown cause. In a study of zinc and lead miners in Oklahoma, they found about 125 cases of typical miliary lung disease among 18,000 persons examined roentgenologically. Many of those with positive roentgen findings were without symptoms, and in only 2 of 88 cases in which sputum examination was done were tubercle bacilli discovered. In 31 cases, however, the presence of fungi identified as *Aspergillus fumigatus fisheri* and *Aspergillus niger* was demonstrated in unstained sputum smears.

Ten years later, Aronson, Saylor, and Parr (1), made a study of Indian children on reservations in Arizona, showing that coccidioidomycosis was probably a factor in the production of calcified pulmonary nodules in negative tuberculin reactors.

Smith (14), in 1943, was among the first to suggest a relationship between histoplasmosis and pulmonary calcification, mentioning in the course of a paper devoted in the main to another subject that the endemic area of histoplasmosis corresponded to that containing many cases of pulmonary calcification among tuberculin negative reactors. Two years later, Christie and Peterson (4), after studying a group of 181 children, reported that histoplasmin reactors were three times more common than positive tuberculin reactors. There were almost twice as many children showing pulmonary calcification as there were positive tuberculin reactors.

A careful study of 3,000 nurses in various cities of the Midwest and in Philadelphia by Palmer (9), reported in the same year, showed histoplasmosis to be widely prevalent in certain states and relatively infrequent in others. In those states where the incidence was high, there also occurred frequent cases of pulmonary calcification, leading Palmer to conclude that a considerable proportion of pulmonary calcification in tuberculin-negative persons is due, not to tuberculosis, but in all probability to histoplasmosis. In a later report, Zwerling and Palmer (16) presented a further study of 6,199 student nurses. Of this number, 698 showed evidence of pulmonary calcification. Tuberculin and histoplasmin tests in these subjects showed 57 reacting positively to tuberculin, 494 to histoplasmin, and 109 to both tuberculin and histoplasmin. Individual lesions, as demonstrated on the x-ray film, however, showed no striking or characteristic features making possible a differentiation between the tuberculin reactors and the histoplasmin reactors, except possibly for bilateral miliary calcification. Of 15 such cases, 13 were tuberculin-negative and 2 tuberculin-positive; 14 were histoplasmin-positive and 1 was negative to both antigens. With so small a series, the authors did not feel warranted in drawing definite conclusions, but they suggested the possibility that histoplasmosis or other similar infection may account for many such cases. Equally striking evidence was obtained in subjects

TABLE I: FIVE CASES OF MILIARY CALCIFICATION OF THE LUNGS PRESUMABLY DUE TO ASPERGILLUS

Case Age	Symptoms and Physical Findings	Skin and Sputum Tests	Bronchoscopy	Roentgenography	Progress and End-Result
Case I A. C. 11	Acute "flu-like" attack. Later, harsh non-productive cough. Substernal pain Râles over both lung fields	Skin: tuberculin negative; *Monilia* and *Aspergillus* positive Sputum: negative for tubercle bacilli; *Aspergillus* and *Monilia* cultured numerous times	Yes. *Monilia pinoyi* cultured	Many isolated circular lesions throughout both lungs, larger and less discrete than those of miliary tuberculosis	In a few months the lesions were more discrete. Calcification became visible in course of one year. Many calcified nodules in four years Well at present
Case II P. C. 12	Acute episode similar to Case I. Residual cough not so severe Coarse râles over lung fields	Skin: tuberculin negative; *Aspergillus* and *Monilia* positive Sputum: negative for tubercle bacilli; *Aspergillus* and *Monilia pinoyi* by culture	Yes. *Monilia* by culture	Multiple small circular parenchymatous lesions throughout both lung fields, similar to Case I	One year later increased nodules more discrete. Some fibrosis. Evidence of early calcification in two years. In four years small discrete calcified nodules. Calcification continued since then Well
Case III W. C. 13	Acute episode similar to Cases I and II. Cough persisted Coarse râles over both lungs	Skin: tuberculin negative; *Aspergillus* and *Monilia* positive Sputum: negative for tubercle bacilli; *Aspergillus* and *Monilia* by culture	Yes. Bronchi thickened and hyperemic, no ulceration. *Aspergillus* cultured	Multiple circular fuzzy lesions throughout both lung fields, similar to Case I	Lesions became more prominent and discrete. Early calcification in eighteen months. Prominent calcification in two and a half years and almost complete in four years. Very dense in nine years
Case IV J. C. 14	Acute episode followed by aching. Violent cough and 7 lb. weight loss Râles over both lung fields	Skin: tuberculin negative; *Aspergillus* and *Monilia* positive. Sputum: negative for tubercle bacilli; *Aspergillus* and *Monilia* by culture	No	Multiple rounded lesions similar to other cases in both lung fields	In one year nodules were much more discrete and dense. Early calcification visible in eighteen months. Very dense and discrete in nine years. Well
Case V W. C. (Mother) 55	Severe cold at time of illness of the children		No	Multiple circular lesions resembling those in the children	Died in an accident one year after infection. Some resolution of the acute changes corresponding to those noted above

showing massive calcification of the hilar nodes, which has long been considered as pathognomonic of a healed primary tuberculous complex. In this group, also, there was a high percentage of histoplasmin-positive and of tuberculin-negative reactors. Pulmonary calcification, the authors conclude, is an end-result of a disease

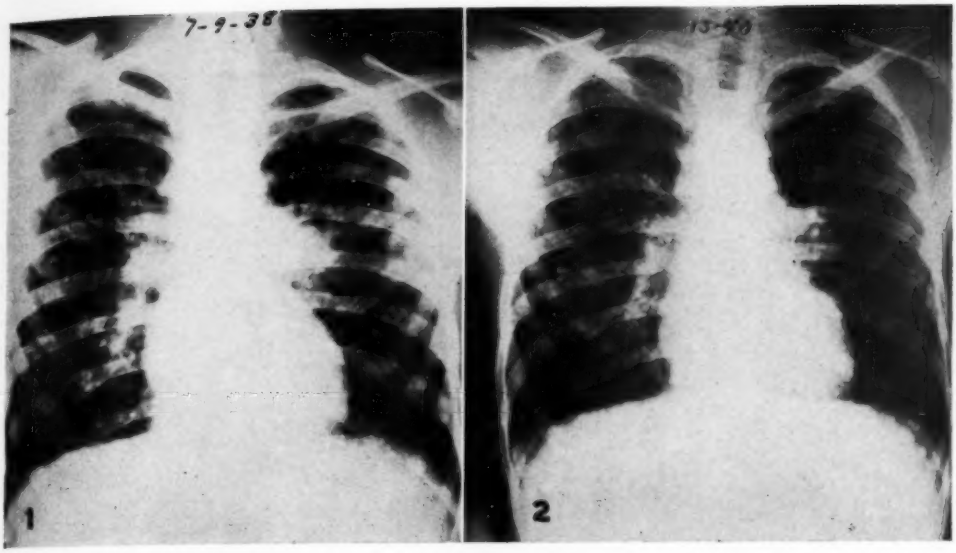

Fig. 1. Case I. Marked hilar enlargement; multiple soft nodular lesions in both lungs. July 9, 1938.
Fig. 2. Case I. Hilar areas smaller; discrete calcified nodules and soft nodules in both lungs. Oct. 15, 1940.

process, and until the disease shall have been studied from the stage of infection to the stage of calcification, it is possible only to draw inferences concerning the nature of the active phase.

A more recent report by High, Zwerling, and Furcolow (6) is based on 113 instances of disseminated pulmonary calcification, including 44 cases (38.9 per cent) of the miliary type and 69 of the multiple bilateral type. Among the 113 patients, 108 were tested with both tuberculin and histoplasmin and, of these, 104 or 96.3 per cent reacted positively to histoplasmin and 4 negatively. Eleven reacted positively to tuberculin but in no instance was there a positive tuberculin reaction only. These figures are believed to offer strong evidence that disseminated calcifications are "not frequently caused by tubercle bacilli, but probably by the agent producing sensitivity to histoplasmin."

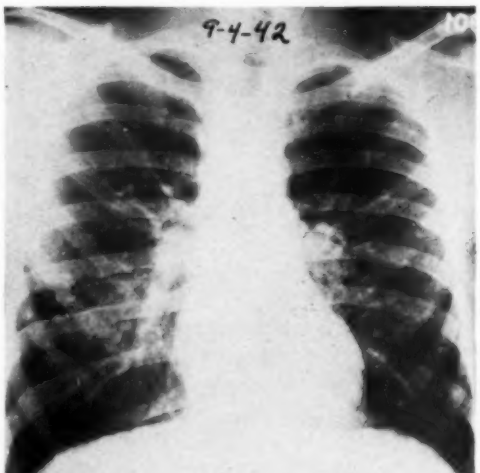

Fig. 3. Case I. Multiple calcified nodules in both lungs; calcified hilar nodes. Sept. 4, 1942.

In the preceding reports by workers in the United States Public Health Service (Palmer; Zwerling and Palmer; High, Zwerling, and Furcolow), a strong case has been made for histoplasmosis as the infectious agent in the production of pulmonary calcification. On the other hand, as shown by Aronson, Saylor, and Parr and others, pulmonary calcification may be an end-result of coccidioidomycosis, and in some sections this may account for a small percentage of the observed cases. Carter

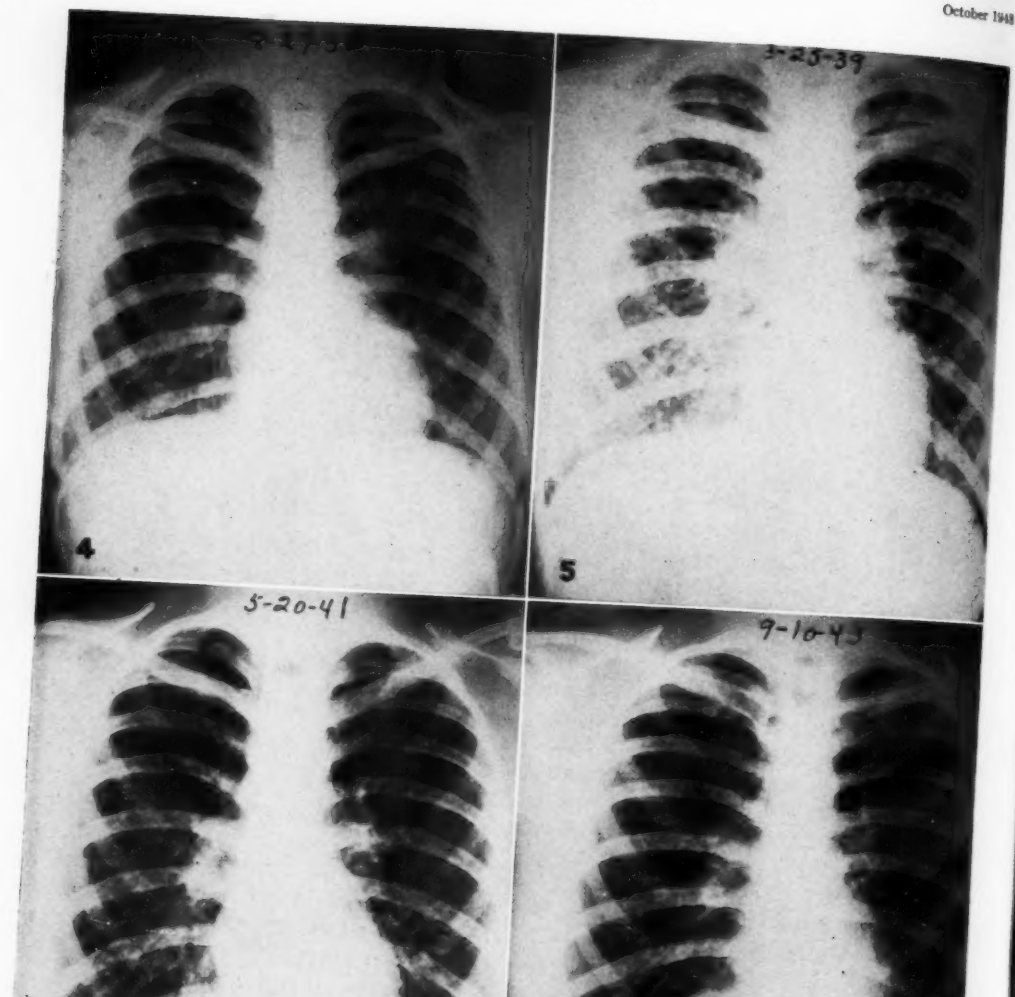

Fig. 4. Case II. Hilar enlargement; multiple nodules throughout both lungs. Aug. 27, 1938.
Fig. 5. Case II. Nodules increased in number and size. March 25, 1939.
Fig. 6. Case II. Nodules more discrete, showing moderate amount of calcification. May 20, 1941.
Fig. 7. Case II. Increased calcification of the nodules. Sept. 10, 1943.

(3) mentions a calcific studding along the bronchial trunks in cases of blastomycosis, originally described by Dunham. Several other mycotic infections are also known to produce pulmonary lesions, which, if followed throughout the entire course of the disease, could well end in calcification.

It has been our good fortune to follow four members of one family with *Aspergillus* and *Monilia* infection of the lungs

continuously for ten years, with frequent roentgen examinations. During this period we have observed the lesions through the successive stages of early infection, resolution, fibrosis, and the final appearance of miliary calcifications which are as definite as any such calcified nodules previously observed by us. We have found no record of any similar series so observed. These cases will be reported briefly here from the roentgenologic standpoint only, as a complete clinical report is now being prepared for publication elsewhere. The details are presented in tabular form (p. 482) for easy comparison.

It will be noted that the group consisted of a mother (Case V) and four children (Cases I–IV) of school age. The mother was followed for only a year. Two other members of the family were not affected. The symptoms at the beginning resembled an attack of influenza, leaving the patients with a severe cough, largely non-productive. Physical examination did not reveal the extent of the lesions, usually showing little more than a few râles over the bases of the lungs. Tuberculin reactions were negative in all cases but, in all, skin tests for aspergillosis and moniliasis were positive. Sputum tests on the four children failed to show tubercle bacilli, but *Aspergillus* and *Monilia* were cultured from the sputum, in some of the cases over a period of several years.

Bronchoscopy was performed on three of the patients. The bronchi were thickened and hyperemic, but no ulceration was found. Cultures were taken, and *Monilia pinoyi* was obtained from two cases and *Aspergillus* from the third. The roentgen picture in all these cases was very similar, showing widely disseminated circular lesions of miliary distribution throughout both lungs. When first observed, shortly after the primary infection, the lesions were larger and less circumscribed than is usual in miliary tuberculosis. A few months later they had become still larger and more distinct, though they were always hazy in outline. There was never any evidence of coalescence or consolidation of the lesions. After reaching the stage of development mentioned above, they changed slowly; the individual nodules decreased in size and appeared to become more discrete and dense. At the end of approximately two years, small calcific flecks appeared in the nodules. With each succeeding year the calcifications became more prominent and uniform in appearance. Those seen in the tenth year are smooth in contour and densely calcified. The patients are now clinically well from a pulmonary standpoint, and one was able to enter the W.A.C. and served without untoward incident.

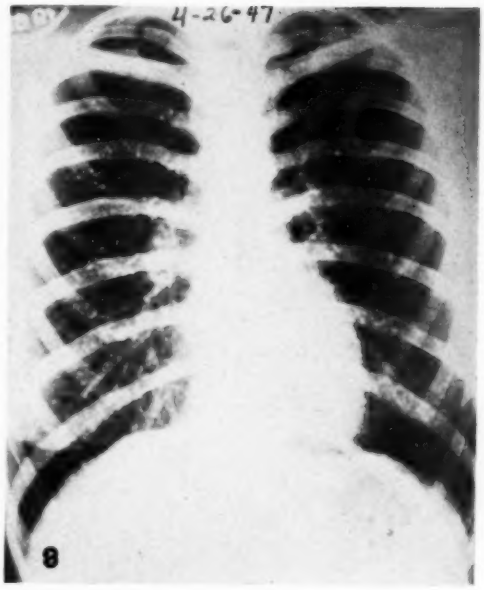

Fig. 8. Case II. The end stage, with complete calcification of the nodules. April 26, 1947.

Occasionally cases of miliary pulmonary calcification are seen in which there is indisputable evidence of tuberculosis in the lungs or in other parts of the body. Two such cases are reported below. In Case VI there was evidence of active pulmonary tuberculosis involving the apices of both lungs, with tubercle bacilli in the sputum and no fungi. Postmortem many small calcified bodies were found in the lungs and in the spleen. In Case VII there were miliary calcified nodules in the

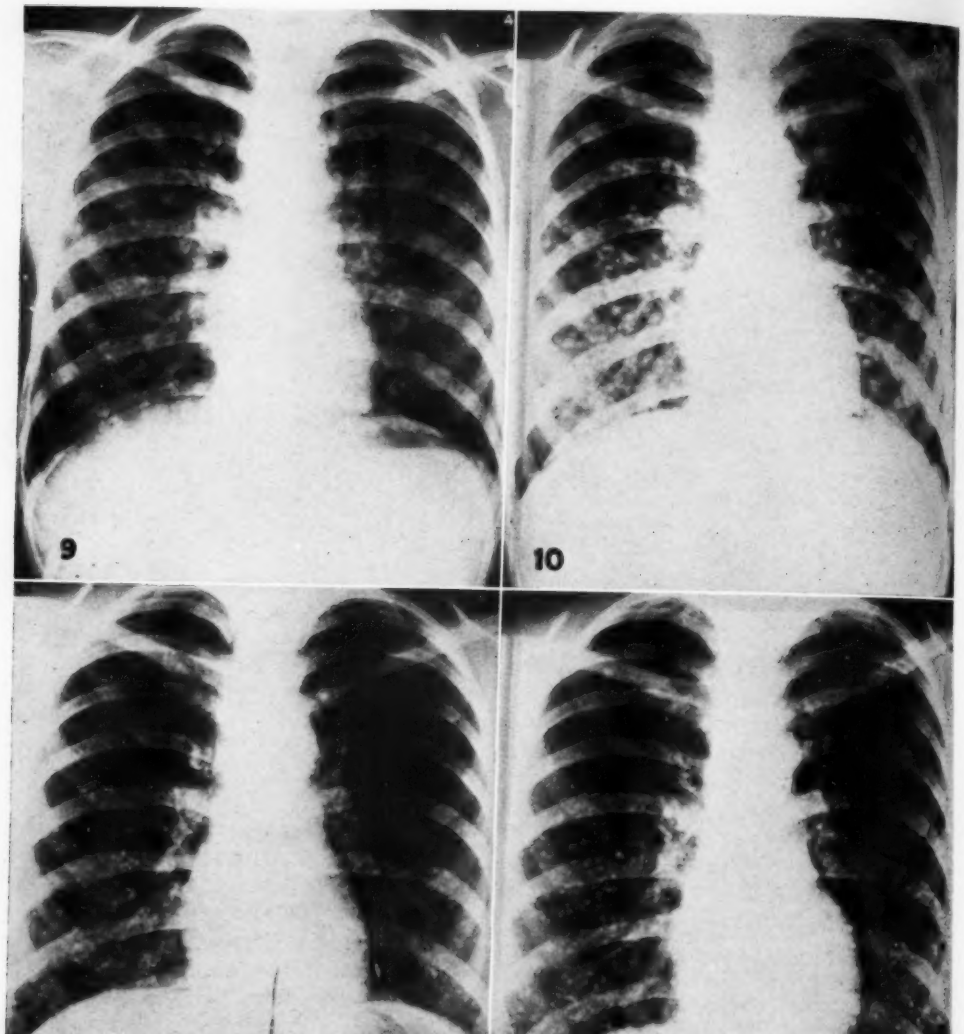

Fig. 9. Case III. Soft nodular infiltration throughout both lungs. April 6, 1938.
Fig. 10. Case III. Increased markings in the bases; some clearing in the apices. July 9, 1939.
Fig. 11. Case III. Nodules more discrete, showing considerable calcification. Dec. 31, 1940.
Fig. 12. Case III. Extensive calcification of the miliary nodules. Sept. 4, 1942.

lungs and evidence of tuberculosis of the epididymis, the right kidney, and probably the right wrist. Death was due to tuberculous meningitis.

These cases are typical of a group in which the evidence appears to favor a tuberculous etiology for the miliary calcified nodules in the lungs. It might, of course, be argued that the miliary calcification is the result of an older healed

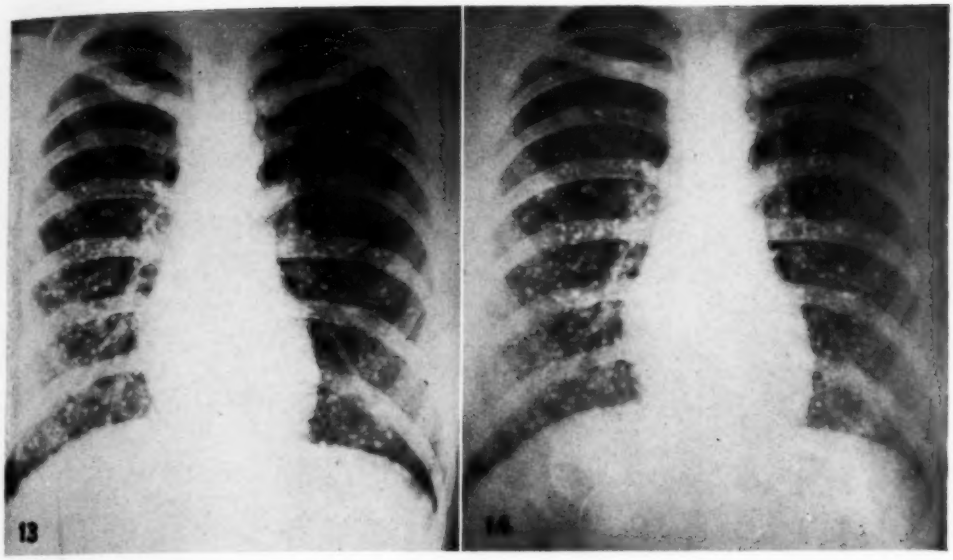

Fig. 13. Case III. Complete calcification of the miliary nodules. Feb. 26, 1944.
Fig. 14. Case III. Complete calcification, nine years after the primary infection. Practically no change since 1944. April 21, 1947.

mycotic infection with a superimposed tuberculous terminal infection. Against this assumption there is no adequate defense except its improbability. Until skin tests for mycotic infections are more widely employed, and more accurate, such problems cannot be scientifically solved.

CASE VI: E. R., a white male, aged 32, gave a history of severe cough with dyspnea for two years. Sputum was abundant and at times blood-streaked. There had been a loss of 20 pounds in weight.

Physical examination showed evidence of impairment at both pulmonary apices with probable cavitation in the left upper lobe.

X-ray examination disclosed miliary calcified nodules throughout both lungs, discrete and densely calcified. There was also an area of tuberculous involvement of the left upper lobe with cavitation, and a small area of infiltration was present in the right upper lobe.

The sputum was positive for tubercle bacilli and negative for fungi.

The course was that of a florid tuberculosis, with death twenty-five days after admission.

Necropsy: The left lung weighed 800 gm. and showed several cavities near the apex. There were cavities also at the right apex. Both lungs contained many small pearly bodies the size of a millet seed. There were several caseous, calcifying nodes at the hilus of each lung. A number of small grayish areas were found in the spleen similar to those in the lungs.

CASE VII: F. S., a white male, aged 57, was admitted because of painful and swollen testicles. Examination revealed evidence of probable tuberculous epididymitis, later proved histologically.

X-ray examination of the chest revealed many calcified hilar nodes together with miliary calcified nodules in both lungs. There was no evidence of recent parenchymal infiltration. Pyelographic study suggested probable tuberculosis of the right kidney. Laboratory examination of a twenty-four-hour urine specimen was positive for tubercle bacilli.

Several months later, swelling developed in the right hand and wrist. Examination showed thickening, tenderness, pain on motion, and inability to actively extend the wrist. A tuberculous synovitis was suggested. X-ray examination revealed marked soft-tissue swelling over the hand and wrist but no abnormal bone changes.

An epididymectomy was subsequently performed in another hospital, and a pathological diagnosis of advanced active chronic tuberculosis with caseous necrosis was made. Later, symptoms of meningitis developed and guinea-pig inoculation of the spinal fluid was positive for tuberculosis. The patient then left the hospital against advice and died at home. No autopsy was obtained.

DISCUSSION

From a review of the literature and from personal observation of the cases reported above, it would appear that miliary pul-

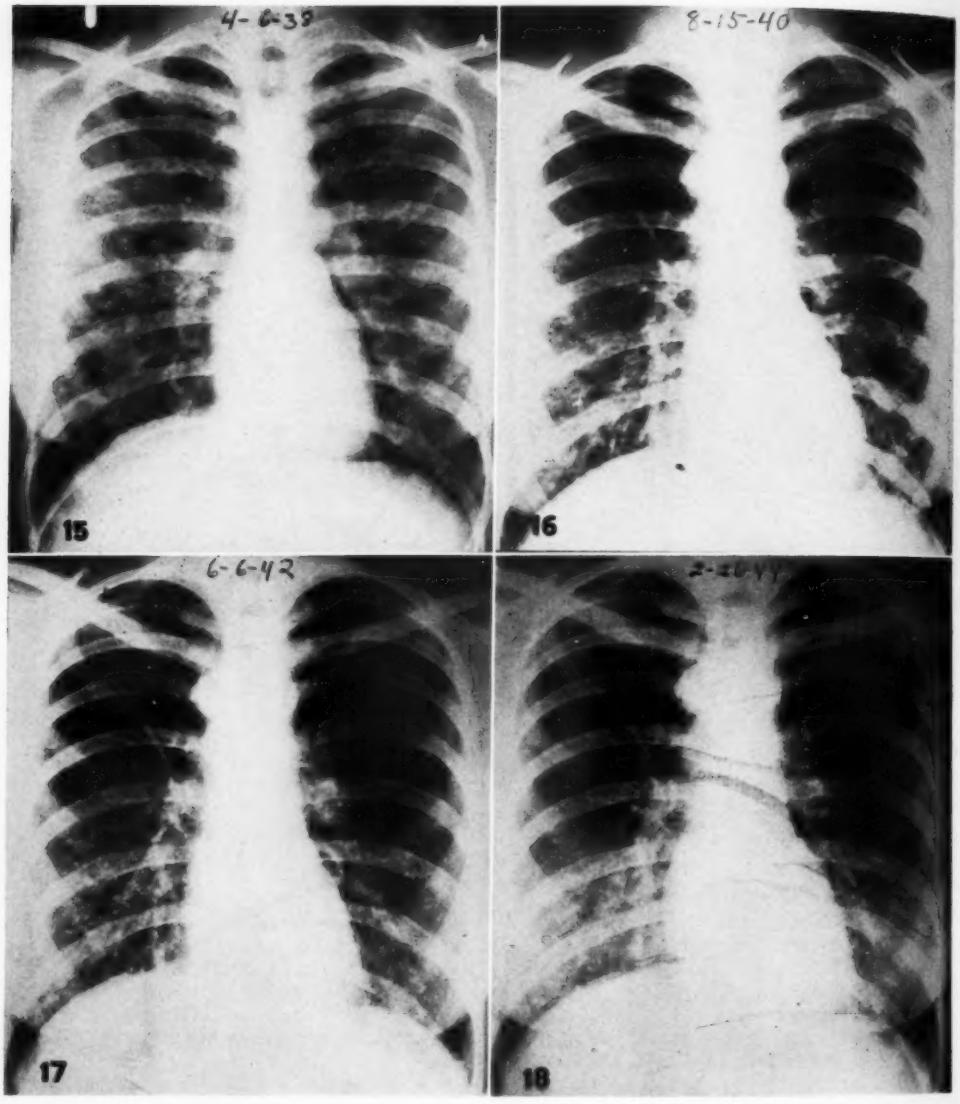

Fig. 15. Case IV. Enlarged hilar nodes; soft nodular infiltrations throughout both lungs. April 6, 1938.
Fig. 16. Case IV. Clearing in the upper areas; discrete nodules with some calcification in both bases. Aug. 15, 1940.
Fig. 17. Case IV. Extensive calcification of the nodules in both lungs. June 6, 1942.
Fig. 18. Case IV. Complete calcification of the nodules six years after the primary infection. Feb. 26, 1944. A film in 1947 shows the same amount of calcification.

monary calcification may be the result of various etiologic factors. As has been pointed out, the earlier investigators believed that it represented a healed miliary tuberculosis, though proof of this, except in isolated instances, was not obtainable. Such proof as was offered consisted solely in the presence of other evidences of tuberculous disease. We know of no case in which tubercle bacilli were cultured from the calcified nodules, which accords with the statement of Blaine (quoted from

Schmauss) that living bacilli are never found in pathological examination of calcified nodules.

The discovery of Sayers and Meriwether of *Aspergillus* in the sputum of miners showing miliary calcified nodules in the

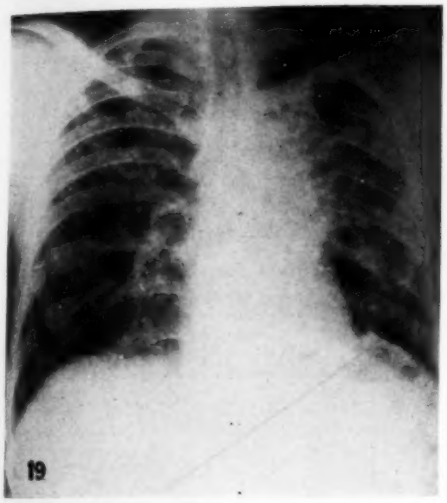

Fig. 19. Case VI. Miliary nodulation throughout both lungs. Recent tuberculous infiltration in both upper lung fields with cavitation in the left upper.

lungs led to the tentative suggestion that mycotic infection might play an etiologic role in the production of such lesions, and subsequent studies by others showed calcifications in association with coccidioidomycosis and blastomycosis.

The most extensive investigations of this problem have been those conducted under the auspices of the U. S. Public Health Service by Palmer, Zwerling, High and Furcolow, showing conclusively that a high percentage of persons with disseminated pulmonary calcification react positively to histoplasmin, while many fail to react to tuberculin.

Our own study of four cases of mycotic infection followed from the earliest stage of pulmonary involvement to the final picture of miliary calcification we believe proves conclusively that such calcification may develop as the result of a mycosis. It is our opinion that in these cases *Aspergillus* was the primary agent and *Monilia* a

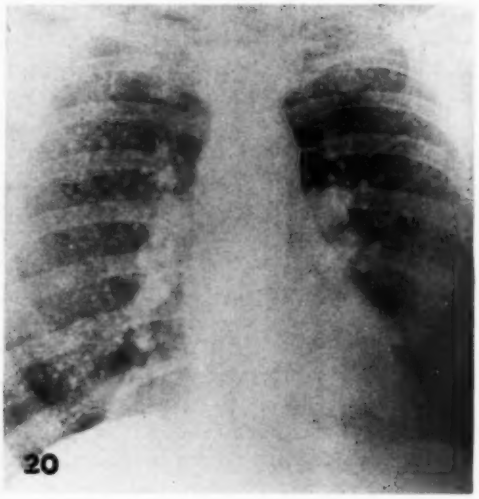

Fig. 20. Case VII. Miliary nodules throughout both lungs with calcified hilar nodes. Numerous extrapulmonary tuberculous lesions. Death due to tuberculous meningitis.

secondary invader, since *Aspergillus* was found in the well water at the home of the patients and was more consistently grown from the sputa. We believe, therefore, that disseminated calcification may result not only from histoplasmosis, but also from coccidioidomycosis, blastomycosis, aspergillosis, moniliasis, and possibly many other mycoses.

The probability that some cases of disseminated calcification are the end-result of tuberculous infection is not, however, to be ruled out. Calcification has been proved to be the end-result in many true primary foci. It is also the end-result of many cases of healed parenchymatous lesions the tuberculous nature of which is indisputable. Pinner (11) has shown that calcified nodules of sharply defined variety may represent the healed stage of a hematogenous (non-miliary) pulmonary tuberculosis. He found this result infinitely more frequent in children and adolescents than in adults. It is also probable that some cases of miliary tuberculosis heal with miliary calcifications as the end-result. This is suggested by such cases as the two (Cases VI and VII) briefly reported above and a number of similar cases to be found in the

literature, though absolute proof is lacking until it becomes possible to follow a series of cases for a period of years, as was done in our series of mycotic infection.

SUMMARY

1. A review of the literature on the etiology of miliary calcification of the lungs shows contradictory findings.

2. The early writers believed that these changes represented a healed stage of miliary tuberculosis.

3. Later investigators found *Aspergillus* in the sputum of a group of cases. Others, on the basis of skin tests only, have presented evidence that histoplasmosis may represent the primary infection.

4. Four cases are reported here of infection by *Aspergillus* and *Monilia* observed for ten years, showing every stage of the disease from primary infection to the end stage of miliary calcified nodules.

5. It would thus appear that mycotic infection can definitely end in miliary calcified nodules in the lungs.

6. It is probable that miliary tuberculosis of the lungs may have a similar end-result in some instances. Two cases supporting this view are briefly reported.

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SUMARIO

Calcificación Miliar del Pulmón: Fases Etiológicas

Un repaso de la literatura relativa a la etiología de la calcificación granúlica de los pulmones arroja hallazgos contradictorios. Creían los antiguos autores que esas alteraciones representaban una etapa cicatrizada de la granulia. Los investigadores subsecuentes descubrieron el *Aspergillus* en el esputo de un grupo de casos. Otros, a base exclusiva de cutirreacciones, han presentado datos en el sentido de que la histoplasmosis puede representar la infección primaria.

Comunícanse ahora cuatro casos de infección por *Aspergillus* y *Monilia* observados durante diez años y que muestran todas las etapas de la enfermedad desde la infección primaria al período terminal de nódulos granúlicos calcificados. Parece pues, que la micosis puede positivamente terminar en nódulos granúlicos calcificados en los pulmones.

Parece probable que la granulia pulmonar termine de modo semejante en algunos casos. Descríbense sucintamente dos casos que apoyan esta opinión. Las radiografías revelan la patología descrita.

Bronchography by Atomization[1]

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ATOMIZATION OF THE opaque medium for bronchography can be accomplished by placing the tip of the atomizer at the larynx behind the epiglottis, in the trachea below the vocal cords, or at the main bronchus.

Technic: We anesthetize the base of the tongue, pharynx, larynx, and trachea by a 1 per cent solution of pantocaine, vaporized, with the patient in the sitting position on the x-ray table. We have tried different opaque media but at present we use 20 per cent lipiodol; usually from 10 to 15 c.c. is necessary. The atomization lasts about two minutes. It is very important to use a good and well timed radiographic technic since all our efforts would be lost if we did not obtain good roentgenograms at the right moment and in the best position.

For supratracheal atomization we place the tip of the atomizer in the larynx behind the epiglottis. During the atomization the patient remains in the sitting position inclined to the side to be explored and leaning forward or backward according to the location of the pulmonary segment to be examined. Immediately after the atomization, he is placed in the horizontal position and, according to the side and pulmonary segments to be explored, the necessary roentgenograms are obtained. For the upper lobes the Trendelenburg position is used.

For atomization at the larynx, a DeVilbiss No. 152 atomizer can be used, but we find a longer one more useful. The atomizer is connected by a rubber tube to an air compressor, such as is employed by the laryngologists, and from 6 to 8 pounds of pressure are used.

For intratracheal atomization we have constructed a long atomizer which permits a very fine atomization, the tip of which

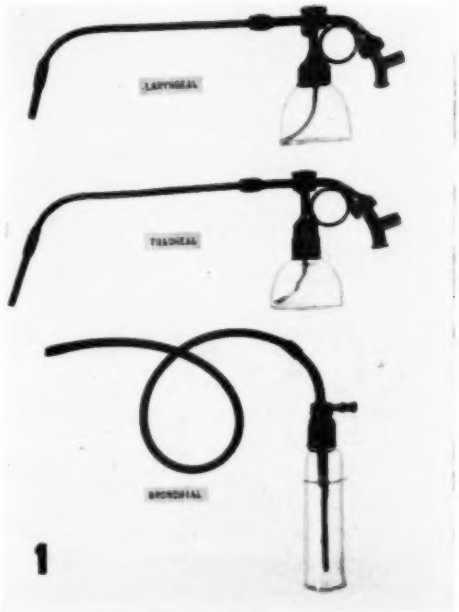
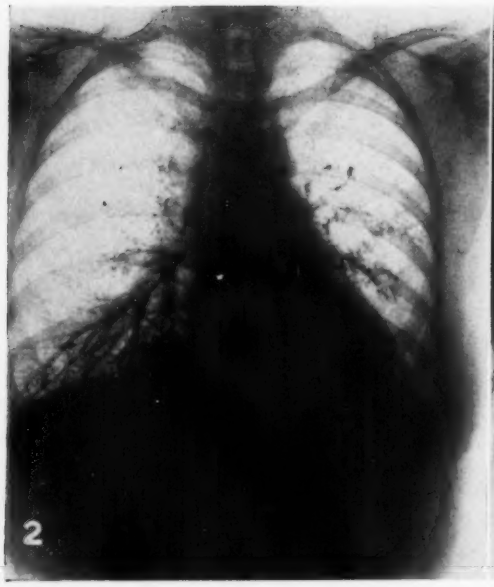


Fig. 1. Different types of atomizers for laryngeal, intratracheal, and intrabronchial atomization.

can be easily placed below the vocal cords with the help of a laryngeal mirror. The atomization is done following anesthesia, with the patient sitting on the x-ray table. Immediately after the atomization he is placed in various positions according to the different pulmonary segments to be explored. The technic is the same as for supratracheal atomization. It is very important to keep the patient from coughing.

For intrabronchial atomization we use a No. 16 rubber catheter, through which we pass a No. 8 urethral catheter. The first carries the air and the second the lipiodol. Both are connected to a small atomizing chamber that we can regulate in order to produce a very fine spray. After anesthetizing the nasal fossa and the larynx,

[1] Presented at the Thirty-third Annual Meeting of the Radiological Society of North America, Boston, Mass., Nov. 30–Dec. 5, 1947.



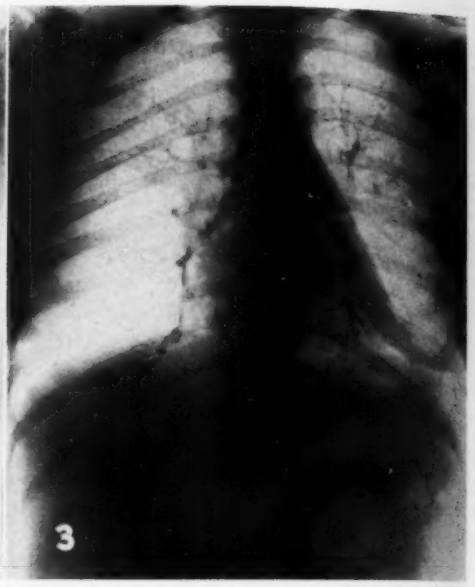


Fig. 2. Postero-anterior view showing the trachea, right and left large and lobar bronchi after supratracheal atomization of 15 c.c. of lipiodol.

Fig. 3. Postero-anterior view showing the large and lobar bronchi after intratracheal atomization of 10 c.c. of lipiodol.

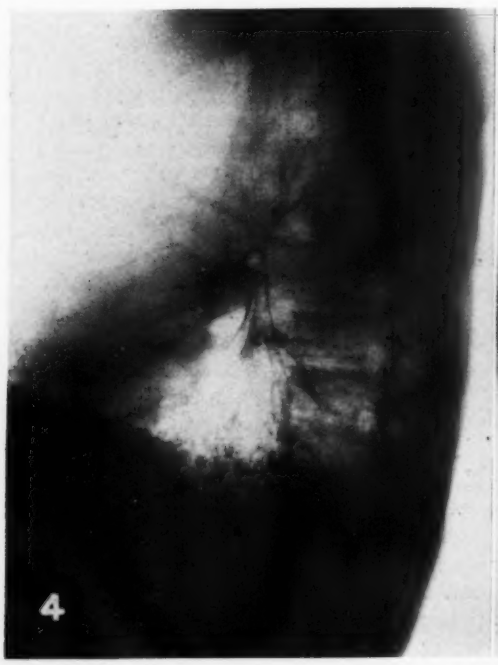


Fig. 4. Lateral view showing all the right bronchial tree after the atomization of 15 c.c. of lipiodol.

Fig. 5. Lateral view after atomizing 10 c.c. of lipiodol, showing bronchial dilatations of the middle lobe.

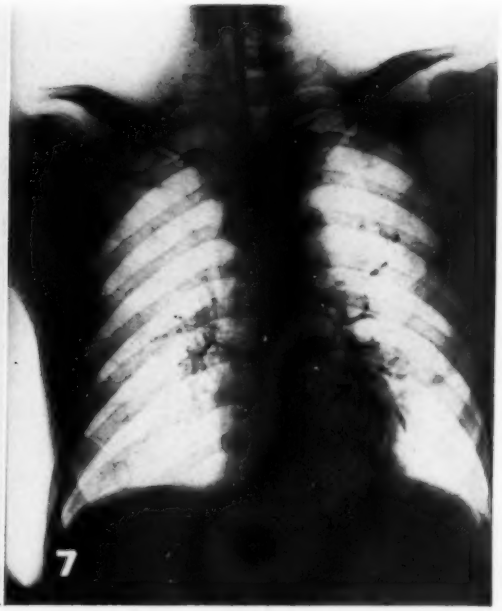


Fig. 6. Postero-anterior view after intrabronchial atomization of 15 c.c. of lipiodol, showing the cavity of a pulmonary abscess in the lower left lobe.

Fig. 7. Lateral view after atomizing 10 c.c. of lipiodol, showing bronchial tuberculosis of the middle lobe with atelectasis.

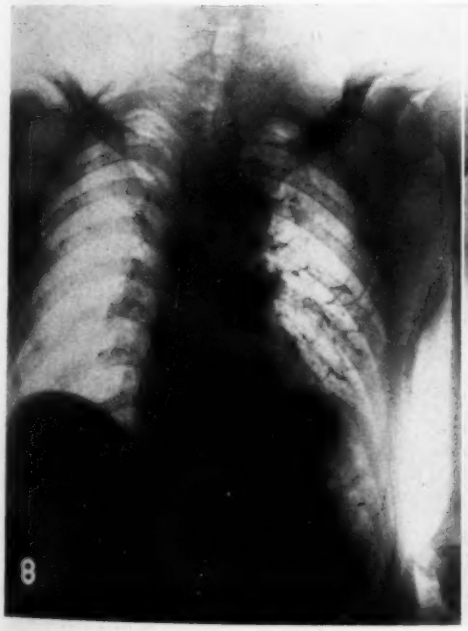


Fig. 8. Postero-anterior view after supratracheal atomization of 10 c.c. of lipiodol, showing a round filling defect with regular borders, due to bronchial polyp.

Fig. 9. Filling defect with irregular borders in the main right bronchus, with complete obstruction of the upper lobe bronchus, due to carcinoma.

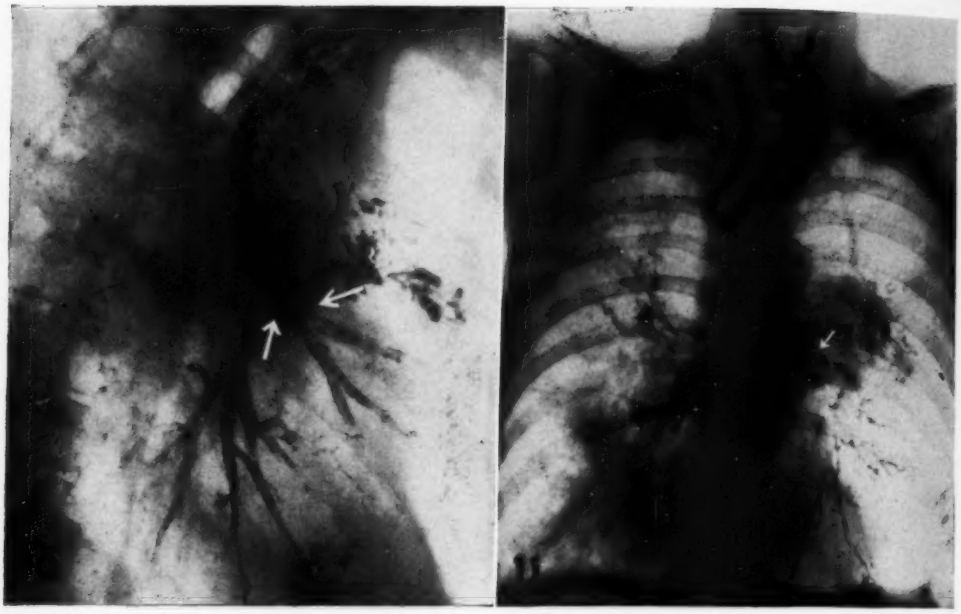


Fig. 10. Very early submucosal infiltration at the entrance of the middle left lobe. No obstruction present.
Fig. 11. Same case three months later, showing the complete destruction of the main left bronchus and the nodular type of tumor surrounding it.

pharynx, and trachea with a pantocaine spray, we pass the catheter through the nose into the trachea. The patient is then taken to the fluoroscopic table and the atomizing chamber is placed in the main bronchus of the side to be examined. We then vaporize the opaque medium in different positions for the different pulmonary segments, and roentgenograms are taken.

Very fine details of the bronchial mucosa may be observed. All the bronchial tree of one side can be examined, films being taken in the different positions for each pulmonary segment. If necessary, the bronchial tree of the other side may be examined after two or three days. There is no considerable accumulation of lipiodol, since the amount used is small and the atomized medium is rapidly eliminated.

When there is a bronchial obstruction, the opaque medium accumulates above the obstruction, giving an image similar to those observed in filling bronchography. When there is no obstruction, the opaque medium reaches as far down as the alveoli, coating the internal surface of the bronchi.

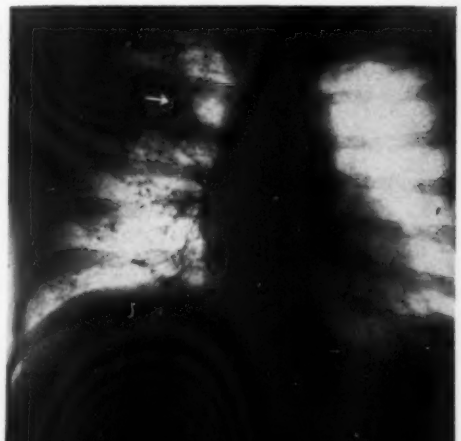


Fig. 12. Bronchial obstruction of the upper posterior segment with nodular type of carcinoma surrounding it.

This method is harmless. We have used it with good results for years in the diagnosis of many bronchial lesions.

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SUMARIO

Broncografía por Atomización

Descríbese la técnica de la broncografía por medio de la atomización del medio opaco. Anestésianse la base de la lengua, faringe, laringe y tráquea con una pulverización de pantocaína (solución al 1 por ciento), colocando el extremo del pulverizador en la laringe detrás de la epiglotis, en la tráquea más abajo de las cuerdas vocales o en el bronquio. Usase lipiodol al 20 por ciento, soliendo bastar con 10 a 15 cc. La atomización consume unos dos minutos, después de lo cual se coloca al enfermo en posición conforme al segmento pulmonar por examinar y se toman las radiografías.

Con esta técnica pueden observarse detalles muy delicados de la mucosa bronquial. Si hay oclusión bronquial, el medio opaco se acumula más arriba de la obstrucción, dando una imagen semejante a las observadas en la broncografía ordinaria. Si no hay obstrucción, el medio opaco desciende hasta los alvéolos, recubriendo la cara interna de los bronquios.

No hay mayor acumulación de lipiodol, por ser tan pequeña la cantidad necesaria y tan rápida su eliminación, y no se han observado resultados desfavorables en muchos años de experiencia.

DISCUSSION

(Papers by Robbins; Mallory; King; Doub; Fariñas)

Aubrey O. Hampton, M.D. (Washington, D. C.): It is certainly a privilege to take part in this program. In spite of some of the apologies that have been offered by the men who have discussed the various phases of idiopathic pulmonary fibrosis, you must not entertain the idea that they are not qualified to discuss the subjects they have talked about. I know that they have worked on the problem at least ten years or longer, and even though a complete answer is not available, I believe that, after careful consideration of their papers, you will appreciate that in so far as information is available, they have given you the accepted facts or theories.

Dr. Robbins is trying, I am sure, to establish a filing diagnosis for a group of cases which fit no other category. I once thought that we had the answer. I thought it would be quite simple to make the diagnosis fluoroscopically, based upon the widening of the trachea at inspiration, the widening of the mediastinum, the paradoxical mediastinum as described by Dr. Robbins, and the sudden limited motion of the diaphragm, but that is not so. Not all the cases, however, show this advanced picture. I thought that we could readily differentiate these cases from other lesions, and that, too, I have found to be impossible.

Attempts have certainly been made at the Massachusetts General Hospital to arrive at an etiological diagnosis from the bacterial standpoint, and no progress has been made. I am a little surprised at my friend, Dr. Mallory. He is usually somewhat more conservative in his proposals and I think, had it not been for Dr. King, you wouldn't believe that Dr. Mallory has suggested that sarcoid produces this picture. I think Dr. King would like to believe it. Dr. Mallory suggests suggesting it. I don't believe it.

The reason I don't believe that sarcoid produces fibrosis is that in all of the cases we have followed with proved sarcoid, there has been no residual scarring in the lung when the lesion healed or when it disappeared, as you might say, and we have followed a large number since 1932.

The pathology I shouldn't discuss, but, as I have viewed a few sections, the specimen shows no evidence of necrosis or of fibrin deposit or fibroblasts. I would like to ask Dr. Mallory how he would jump to the conclusion, let us say, that this lesion produces scarring when it produces no destruction and no fibroblasts are to be found within it.

I would like to discuss, also, the frequent mention of unresolved pneumonia and organized pneumonia in this presentation. It does not mean that these pathological processes are the least bit frequent. In fact, I have heard Dr. Mallory report a case at conference in which he said, "This is the first case of unresolved pneumonia I have seen in ten years; in fact, it is the only one that I have ever seen."

I hope that he will stress that point. Organized pneumonia would seem to me to be a conclusion drawn only from looking at the histologic specimen. There is no proof in any of these cases that pneumonia had occurred; at least, there is no x-ray showing such findings.

The dilatation of the bronchi in the fibrotic lung I think confirms Dr. Fleischner's theory and, what I believe to be a fact, that these changes

do produce bronchiectasis; that the bronchi are, for the most part, intact; that in addition to that they are even thin-walled—they don't show the slightest evidence of infection; and if you use some of the pathological material presented by Dr. Mallory and correlate it with Dr. Fleischner's ideas, I think you can understand more clearly the reasoning of both.[1]

It is interesting to me that bronchiectasis does not change in spite of the definitions saying that it is a chronic progressive, suppurative disease of the lung. That should further support Dr. Fleischner's argument that the disease is not primary in the bronchus. I have seen follow-up films of bronchiectatic lungs over ten-year periods and you can superimpose them. There was absolutely no change.

Unfortunately, I haven't had enough of these cases that I could follow. The surgeon doesn't permit a very long follow-up on them these days. There is a group of bronchiectatic lesions where the surrounding lung is emphysematous. That group is very difficult to explain unless you assume that the emphysema is due to lung destruction and a replacement compensatory emphysema. Then there would still be traction, but as you view the films, they appear to show the lobe even larger than normal. I think it is more likely that the lobe remains at inspiration because it does not expand and contract; it seems to be larger than normal. There must still be a decrease in intrapulmonary pressure.

The discussion of Dr. Doub I know nothing about. I don't know how pathogenic these organisms are. It has been my opinion that they are not sufficiently pathogenic to produce clinical illness. Whether they will produce lesions which later lead to calcification is another matter. The only experience I have had with miliary calcification has ended in a postmortem examination offering no explanation. There was nothing there except calcification.

Le Roy Sante, M.D. (St. Louis, Mo.): I hardly know where to begin my discussion of these papers. As a matter of fact, I have no quarrel with the essayists on any point other than the title. I think that it is a bit misleading to say "Idiopathic Pulmonary Fibrosis and Pulmonary Emphysema"; "idiopathic" here seems to apply to a form of fibrosis which apparently occurs in a form of disease that hasn't yet been described, or at least evaluated. If it were stated that a peculiar type of fibrosis associated with a granulomatous form of pulmonary disease was to be discussed, I think that that would leave a clearer impression in the mind of the average radiologist as to just what the author was driving at; that there really was something new in his presentation; that this type of fibrosis was something heretofore undescribed.

Fibrosis is a process by which damage is repaired, damage that is due perhaps to trauma, to infection, to irritation, to many other causes. It seems to me that Dr. King enumerated them very logically and very well. Even passive congestion, occurring repeatedly, produces fibrosis. The point is that healing by fibrosis is a process with which we are familiar in widely varying types of injury to the tissues.

Now this new pathological observation made by Dr. Mallory suggests another type of fibrotic deposit associated with granulomatous lesions, having unusual clinical as well as roentgenologic findings.

In view of the many bizarre types of infections of the lungs that we are now seeing and that we are calling, for want of a better term, atypical pneumonias, it may be possible that there are many conditions which we have overlooked in the past, of unknown etiology, which, when their true nature becomes known, will be readily understood and recognized.

The roentgenographic studies presented by Dr. Robbins seem to illustrate better than anything else, the thought which he is trying to expound. We have all seen cases, such as he points out, in which there were rather large, diffuse areas of fibrosis occurring in the lungs of individuals for which there was no demonstrable cause. It is possible that, if we follow up such cases, these findings can be substantiated and further information obtained as to their identity.

At any rate, it would seem that the observation is very well founded; that it has developed in a field in which we thought the book had been closed. Such a research, developed by the cooperation of three departments, is very worth while and I am sure that future data will clarify the facts and give us better information about the condition.

Dr. Doub's paper on the etiology of miliary calcification in the lung brings to mind an earlier conception of these conditions. Many years ago we used to think of these as possible manifestations of healed forms of miliary tuberculosis and, in fact, the reference which he made from my paper was to "forms *suggestive* of healed miliary tuberculosis"; no positive statement was made because we never had any actual proof of the existence of such a lesion. The lack of any previous history of severe systemic infection in many cases soon dispelled this idea of healed miliary tuberculous lesions and gave us rather the impression that we were dealing with multiple foci of primary tuberculous inoculation, such as are seen in Ghon's phenomenon, terminating in multiple points of calcification throughout the lung parenchyma.

Of course, we have all run across cases of these miliary calcifications in the lung. As a matter of

[1] Dr. Fleischner's paper, "The Pathogenesis of Bronchiectasis," to be published later.

fact, one can sort his cases, starting with two or three calcified nodules, then a half dozen, finally progressing with more and more calcareous deposits, increasing to hundreds and even thousands, until the entire lung field is filled. This would suggest that it is possible to have multiple primary tuberculous foci, perhaps up to the point of widespread tuberculous nodules, as a manifestation of Ghon's phenomenon.

At that time we used to think of tuberculosis as being practically the only condition which terminated with calcification in the lung. Now we know that many fungus infections actually produce calcification. By and large, however, we must not forget that tuberculosis still remains the most outstanding cause of calcified deposits as the end-result of healing.

There are many other diseases which will cause multiple calcified nodules in the chest. Many years ago demonstration of *Aspergillus* in the sputum of some of these patients led to the suspicion that the fungus might be responsible. Calcification associated with *Aspergillus* infection had, of course, long been recognized, in so-called pigeon-feeders' disease, especially in France, where it is customary among pigeon raisers to force-feed the birds by taking a handful of wheat in the mouth and blowing it down their throats. I do not know, however, of any instance in which *Aspergillus* has been cultured from cases having these miliary calcified nodules since that first report, until Dr. Doub's study. The four cases which he has followed for many years from the period of involvement by tiny non-calcified lesions, through to actual calcification, represent the development of a condition that is exactly the same as those we have observed.

We have had two such cases in which miliary nodules throughout both lung fields finally calcified after many years, but we have no proof of the character of infection. This was some twenty years or so ago and we were not able to secure positive fungus growths; in those days the culture of *Aspergillus* and of other fungus infections had not advanced to the point of present perfection. At any rate, we watched these patients—both young children—in whom miliary soft lesions were present throughout the lungs. The appearance was very similar to miliary tuberculosis but clinically the patients did not show evidence of unusual illness. Over a period of years (about fourteen in one case) we noted the development of very tiny, indistinct, pin-point calcified deposits throughout the lungs, becoming somewhat larger but never attaining the size of the lesion we usually see in these cases. It seems to me that Dr. Doub's presentation is a real contribution to our understanding of this subject.

In recent years, largely through the researches of the United States Public Health Service, attempts have been made to relate multiple calcifications in the lungs with *Histoplasma* infection. This is done largely by skin tests using histoplasmin antigens. One difficulty, however, is that no one, as far as I know, has ever demonstrated a case of chronic histoplasmosis which terminated in calcification. All proved cases that I have seen were acute and all were fatal. The crux of the situation is, of course, the specificity of the antigen. This research however, presents a novel method of procedure which deserves fullest consideration. It seems to me that it is well worth while following up, but I don't think as yet that there is any actual proof as to the etiology of the fungus calcifications.

Now as to the paper of Dr. Fariñas: We are all acquainted with his outstanding work in bronchography. It surpasses almost anything I have ever seen, due to his meticulous care and attention to the subject. Now he presents another method of filling the bronchi, not one that is entirely new, since insufflation of bismuth powder was used by Chevalier Jackson long before lipiodol was introduced. This is merely another means of introduction of lipiodol into the lung. By this means the mucosal surface of the trachea and bronchial tree is coated by opaque oil. Even the alveolar structures are outlined without using such large quantities of lipiodol. I am especially impressed by its usefulness in coating the larynx and the upper air passages, the trachea, etc. It really opens a much brighter outlook in that particular region than any other; it should be a welcome aid in diagnosis of laryngeal and upper tracheal lesions.

The amount of lipiodol that is left in the alveoli is very small and should be rapidly absorbed, thus removing the one objection that has been present in lipiodol studies.

There is one question I would like to ask Dr. Fariñas. I noticed he used a 20 per cent lipiodol solution. Is this a solution that is supplied for the purpose, or does he dilute the lipiodol and, if he dilutes it, what form of oil does he use for dilution? Is it poppyseed, sesame, or some type of highly refined vegetable oil? If some such vegetable oil is not provided, I would caution any who might try the method against dilution of the lipiodol with ordinary olive oil or, indeed, with any other type of oil.

It is quite customary, as you know, for nose and throat men to dilute lipiodol with olive oil fifty-fifty, for injection into the antrum; in this locality it causes no difficulty at all, but introduction of the oil into the chest, even vegetable oil (which is the least harmful of any of the oils), if it has not been thoroughly refined and if all fatty acids are not removed, is dangerous even in small quantities.

At first I had thought that Dr. Fariñas used a nose and throat atomizer with quite a high pres-

sure. Too high air pressure can be dangerous. There are many cases on record of men filling tires (though I don't suppose this is quite comparable because of the difference in the pressure) with the pressure hose, who have had a little cut on the finger and, with the release of the terrific air pressure (even without contact) have suffered a subcutaneous emphysema and spread of infection to the whole hand in just an instant. So that at least the pressure should be guarded, especially in use of the supraglottic method, in which the insufflation is at the orifice and not into the trachea itself. I see now that the author uses a hand atomizer; if that is sufficient to vaporize the oil, it would seem to be relatively safe.

Dr. Fariñas (*closing*): The lipiodol is sold in two forms—40 per cent and 20 per cent. It is already prepared by the company.

As to the pressure, we use only 6 to 8 pounds. We have been using this method since 1942, and no accidents have occurred.

Dr. Mallory (*closing*): Nothing is idiopathic as soon as it is explained. The term "idiopathic" here was suggested to us; it was not our choice, and we picked those cases which clinically or radiologically could not be given an etiologic diagnosis. Therefore, a number of other things were included besides this granulomatous pneumonitis, which, so far as I am concerned, still remains idiopathic.

Dr. Hampton raised the question of the infrequency of organized pneumonia. I would agree with that. It is extremely rare to see an unresolved lobar pneumonia. With bronchial pneumonia it is a little commoner and particularly in patients with asthma—then it becomes significant.

These patients with pulmonary fibrosis with histories of chronic asthma also, for the most part had rather definite histories of repeated episodes of pneumonia. The granulomatous group had no such history. The degree of fibrosis in some of these patients when they first presented themselves to the hospital was quite astonishing. The process must have been going on for a great number of years; in at least one case we know that it was going on for better than ten years.

In spite of the acute progression which was still present in all cases at the time of autopsy, the patients had none of the systemic signs that go with an infection—significant fever, chills, sweating, leukocytosis, etc.

I made no effort to cover the literature on pulmonary sarcoid. I find it extremely confusing and am quite unable to interpret a large proportion of the case reports. In many of the cases which have been reported there have been caseous lesions besides the non-caseating ones. Some of the patients have been proved to have active tuberculosis. I don't know how one could, with any certainty, distinguish a sarcoid lesion in the presence of known tuberculosis. In the six cases we have here, there is apparently no evidence of tuberculosis.

I should like once again to emphasize that there is no picture of sarcoid which we can histologically rely on for diagnosis. We have all known this; we have had it called to our attention quite vividly in the last year or two by the appearance of beryllium poisoning, and many of those cases, as you know, have been reported as sarcoidosis. I am at a loss to explain, just as Dr. Hampton is, why sarcoid in the lung should produce severe fibrosis when it apparently does not elsewhere in the body.

I have seen fibrotic healing of sarcoid lesions in lymph nodes—early stages of it—but I don't know that I could yet recognize the healed stage of sarcoidosis of a lymph node.

Roentgen Therapy of Carcinoma of the Lower Lip[1]

J. A. DEL REGATO, M.D.
Columbia, Mo.

SIMPLE SURGICAL excision or cheiloplasty, interstitial or surface curie therapy and roentgen therapy have all been applied with success to the treatment of carcinoma of the lower lip. When adequately administered, all of these treatments are equally capable of controlling the disease; but roentgen therapy is the most capable of adaptation to the circumstances of each case in order to contribute the best esthetic result, in addition to control of the tumor.

A simple V-shaped excision may be preferred for the treatment of very small tumors not requiring removal of more than one-fourth of the free border of the lip. This procedure is effective in controlling small lesions, is followed by negligible impairment and, in addition, is expeditious. Surgical excision may be preferred, also, in order to avoid delay in the surgical care of metastases that are already present; in such cases the esthetic result should be a secondary consideration. Also, in advanced lesions that have already produced a large defect and in which plastic surgery may be ultimately required, the surgeon will be more capable of planning the cosmetic procedure if he handles the case from the beginning.

The use of radium in surface applications is most successful in the treatment of small lesions and those of moderate size. The careful construction of special molds, the assiduous planning and constant surveillance that are required for successful curie therapy would be justified if the same and better results were not obtained with relative ease by other methods. Interstitial curie therapy is to be proscribed, for it is invariably followed by unduly marked atrophy and offers no special advantage. Five years ago we discontinued using radium in our hospital, in the treatment of carcinomas of the lower lip, in favor of roentgen therapy, or, in the earlier lesions, of surgery.

TECHNIC OF ROENTGEN THERAPY

Kilovoltage, filtration, size of field, protraction, daily and total dosage can all be put to play to advantage in order to obtain the best results in the treatment of carcinoma of the lower lip.

As a preliminary step to the treatment of these lesions, the patients are relieved of all teeth in bad or questionable condition; infected teeth on the mid-line of the mandible may later be the cause of radionecrotic complications of the gingiva or bone. In addition to this precaution, a heavy lead shield is always introduced behind the lip, during the course of treatments, to avoid unnecessary irradiation of the oral cavity.

Small carcinomas of the lip can be controlled by the administration of radiations from low-voltage equipment. Most of our patients were treated with a 110-kv. unit. In carcinomas that involve more than one-half of the lip, however, and in those that extend to the buccal mucosa or to the mandible, and in diffuse recurrences following inadequate treatment, the use of radiations of 200 to 250 kv. is preferable. The reason for this choice is qualitative.

A single application of unfiltered radiations is capable of controlling carcinoma of the lower lip, but in the small lesions in which this procedure would be justified, we prefer a surgical excision. The application of unfiltered radiations on mucous membranes often results in marked atrophy, visible defect, and late superficial necrosis, which increases with the size of the field. We prefer to use filters of 0.25 mm. of cop-

[1] From the Department of Radiotherapy, The Ellis Fischel State Cancer Hospital, Columbia, Mo. Presented at the Thirty-third Annual Meeting of the Radiological Society of North America, Boston, Mass., Nov. 30–Dec. 5, 1947.

per for 110 kv. and of 0.5 mm. of copper for 220 kv.

Carcinomas measuring 1 to 2 cm. in diameter, particularly when exophytic in type, may be treated in eight to ten days with excellent results; but for larger lesions it is more satisfactory to protract the treatments over longer periods, to a maximum of six weeks. A daily treatment is preferable.

Depending on the size of field, the quality of radiations used, and the contemplated protraction, treatments are started with a dose which may vary from 100 to 300 r (measured in the air at the surface of the lip). In short treatments of one to two weeks, the same daily dose may be repeated from beginning to end. In longer treatments, it is preferable to increase the daily dose several times during the treatment; while secondary infection and inflammation are reduced and the tumor shrinks, successive adjustments of the size of the field are made to reduce its area to a minimum toward the end of the course of treatments. In the case of relatively undifferentiated carcinomas, a field too narrowly adjusted to the size of the lesion may result in early recurrences on the border of the field.

Any statement of dosage that is not accompanied by considerations of quality of radiations, thickness of irradiated tissues, size of field, filter, etc., is at best misleading. A statement of tumor dose is most desirable, but the rate at which this dose has been accumulated and the total protraction of treatments in time are of equal importance; an expression of quality of radiations absorbed by the tumor and surrounding tissues is also important but seldom possible. The dose delivered in our cases varies from 3,000 to 7,000 r (measured in the air at the surface of the lip). The dose is larger, of course, the greater the protraction.

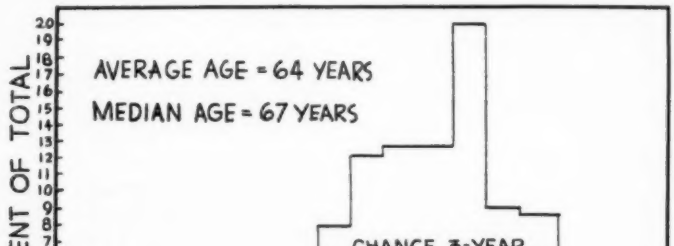

Fig. 1. Age distribution of 195 patients with carcinoma of the lower lip, subject of this report.

The radioepithelitis of the mucous membranes and radioepidermitis of the skin which result from adequate roentgen therapy should extend well beyond the palpable or visible limits of the tumor (Fig. 3). Careful attention should be given to the care of these reactions if complications are to be avoided. Atrophy, fibrosis, telangiectasis and achromia may be reduced to a negligible minimum if these reactions are kept free from secondary infection until the epithelium has been entirely repaired (Figs. 4 and 5B).

TREATMENT OF METASTATIC ADENOPATHIES

Carcinomas of the lower lip metastasize much less frequently than carcinomas arising from other anatomical structures of the oral cavity. Of 152 patients that came

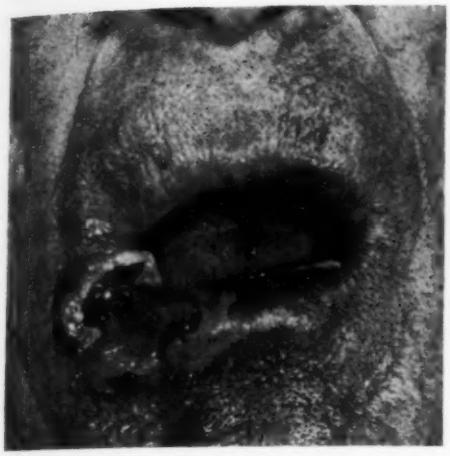

Fig. 2. Epidermoid carcinoma of the lower lip extending from the buccal commissure to near the midline, measuring 3.5 cm. in transverse diameter.

Fig. 3. Moist radioepidermitis of the skin extending well around the limits of the tumor after completion of roentgen therapy that lasted thirty-three days.

to our hospital having had no previous treatments, only 4 (2.6 per cent) presented clinically ostensible metastases on admission; of 43 patients who came with recurrences after various treatments given elsewhere (zinc chloride paste, surgery, curie therapy, roentgen therapy), 9 (21 per cent) presented metastases on admission; the total incidence of clinically ostensible metastases on admission, in 195 cases, was 6.6 per cent. This contrasts markedly with the higher incidence of metastases observed in patients with carcinoma of the tongue, lower gingiva, and the floor of the mouth.

In the majority of cases, the first node affected is a prevascular node in the anterior submaxillary area; bilateral metastases are observed in lesions of the middle third of the lip and also in undifferentiated carcinomas regardless of site; submental and facial node involvement are less frequent. Metastases remain localized to a single node for a considerale time; jugular chain involvement is secondary to submaxillary implants and is observed only in advanced cases or in the rare extremely undifferentiated carcinomas.

A partial upper neck dissection is the treatment of choice of these metastatic lesions; even the bilateral operation carries little risk. In very few instances a radical neck dissection may be preferable; when the metastatic nodes have become adherent to the mandible, a combined jaw resection and neck dissection often succeeds in controlling the disease (5).

Fig. 4. Result of roentgen therapy. Note slight sequelae aside from the defect left by the tumor.

In order to be effective in the treatment of metastatic carcinoma, radiotherapy needs to be applied rather forcefully. Treatment of these metastases by means of radiations is not justified unless surgery is not practicable.

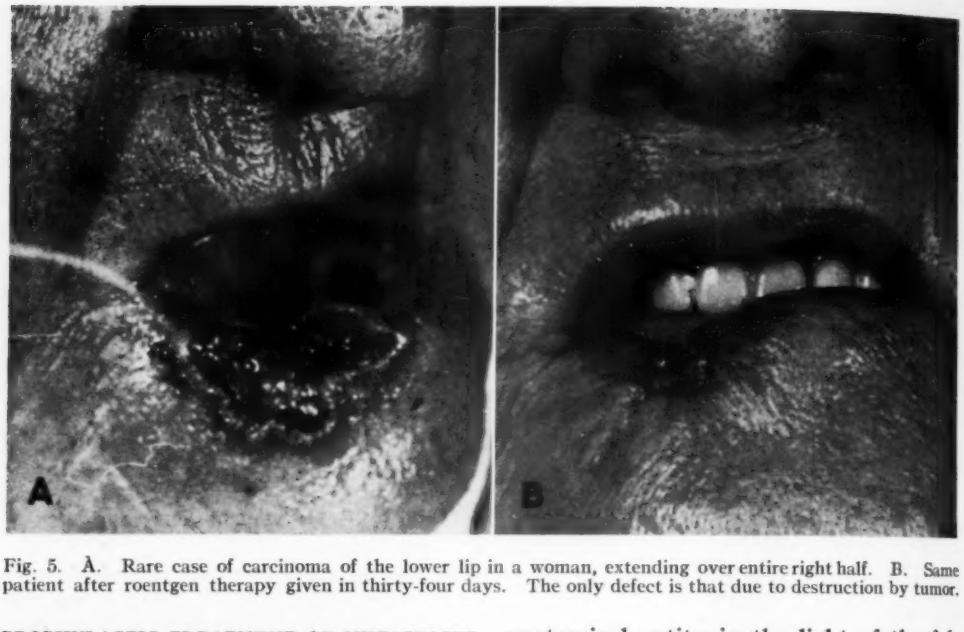

Fig. 5. A. Rare case of carcinoma of the lower lip in a woman, extending over entire right half. B. Same patient after roentgen therapy given in thirty-four days. The only defect is that due to destruction by tumor.

PROPHYLACTIC TREATMENT OF METASTASES

Prophylactic treatment is the institution of therapy in patients without clinical evidence of metastases; this is usually advocated in the hope that it may result in early treatment of metastases that are already present, in a subclinical stage, and that by this early treatment a greater number of such cases may be controlled. Unfortunately, small doses of radiations do not have the gift of preventing the development of metastases. Large doses capable of controlling metastatic carcinoma would not be justified as a routine measure. This discussion is therefore limited to the relative merits of prophylactic neck dissections; the question is whether or not this procedure is justified by the number of cases that are actually found to have metastasized and whether or not the advantage, if any, of such early treatment is nullified by the risk run by all patients and by the proportion of failures to control the primary lesion. It is an error, however, to analyze the issue of prophylactic neck dissections for all carcinomas of the oral cavity, regardless of point of origin. We have proposed (4) that the question be considered for each anatomical entity in the light of the following considerations: (*a*) the chances of permanent sterilization of the primary lesion through adequate treatment; (*b*) the percentage of patients that, not having a clinically ostensible metastasis at the time of treatment of the primary, will present one later; (*c*) the percentage of patients that are lost through inoperability when the metastases are allowed to become clinically evident before they are treated; (*d*) the operative mortality of the proposed operation. (*e*) a comparison of the cure rate of prophylactic neck dissections (when nodes are found invaded) and of therapeutic neck dissections (on nodes that have become clinically ostensible).

Of 148 patients who were referred to our hospital without apparent evidence of metastasis, 11 (7 per cent) presented metastases within a few months; of 34 additional patients who came with a local recurrence from treatment given elsewhere but without clinical evidence of metastasis, 2 (6 per cent) also presented metastases later. This low incidence of subsequent metastases is in itself a serious contraindication to routine prophylactic neck dissection in carcinomas of the lower lip, even

though the operative mortality and proportion of local failures be very small; in addition, few cases are lost through inoperability due to tumor, and the proportion of cases that are cured by early operation is not much greater than when the operation is delayed (1, 2).

The incidence of metastases from carcinomas of the lower lip bears a definite relationship to the degree of anaplasia and the size of the primary lesions (Tables III and IV); the proportion of metastases is greater in patients with a history of previous unsuccessful treatments (Table II). This knowledge should help in deciding upon the advisability of *elective prophylactic neck dissections* in a few cases; in most instances, however, the assurance of a close follow-up and frequent examinations are sufficient safeguards. When a therapeutic neck dissection is done for metastatic nodes from a lesion of the middle third of the lip, or for a histologically undifferentiated carcinoma, a prophylactic suprahyoid dissection may be indicated on the opposite side.

Follow-up examinations should be done frequently during the first eighteen months after irradiation. The presence of a small palpable node is never decisive, but frequent palpation of the potentially metastatic areas should reveal the growth of the metastatic node that is usually anteriorly situated in the submaxillary region. Submental metastases hidden beneath the mandible may be missed in a cursory palpation; the same is true of facial node metastases that may adhere to the lateral aspect of the mandible at the level of facial vessels, develop slowly, and present as a primary bone lesion, or may ulcerate the skin and give the impression of a peripheral recurrence.

The argument that a prophylactic neck dissection should be done, in most cases, because of the uncertainty of the patient's return, is not justified. Neck dissections are no substitute for adequate follow-up.

RESULTS

From May 1940 to December 1944, 195 patients with carcinoma of the lower lip were referred to the Ellis Fischel State Cancer Hospital; only two of these were females. The majority presented well differentiated carcinomas. Forty-three of these patients had local recurrences from various forms of treatment given elsewhere (zinc chloride paste, radiotherapy, surgery); the proportion of relatively undifferentiated carcinomas and percentage of metastases present were considerably greater in the latter group.

Fig. 6. A. Extensive subcutaneous recurrence of a carcinoma of the lower lip, measuring over 5 cm. in transverse diameter, after application of zinc chloride paste. B. Same patient three and a half years after roentgen therapy administered in forty-five days.

Eight of these 195 patients could not receive any form of curative treatment; 17 received surgical treatment only; 52 with small and moderate-sized lesions were chosen for surface curie therapy, and the remaining 118 patients were treated by roentgen therapy. Doctor T. P. Eberhard, now of the Jefferson Medical College, personally planned and directed all of the radium treatments; he also treated many of

TABLE I: RESULTS OF TREATMENT OF PATIENTS WITH CARCINOMA OF THE LOWER LIP PRESENTING NO CLINICAL EVIDENCE OF METASTASIS AT THE TIME OF TREATMENT

Form of Treatment	Number of Patients	Well 3 Years or More Without Recurrence or Metastasis	Number of Local Recurrences	Subsequent Metastasis Without Recurrence	Died of Intercurrent Disease Before 3 Years	Total 3-Year Surviors	Absolute 3-Year Survival	Normal Chance of 3-Year Survival of Group*
Surgery	12	10	1	..	1	10	83%	88%
Curie therapy	51	41	1†	4	6	44	80%	84%
Roentgen therapy	116	80	8‡	7	21	89	75%	84%
All treatments	179	131	10	11	28	143	80%	84%

* Calculated on the basis of charts that were graciously submitted by Mr. Louis I. Dublin, Vice-President, Metropolitan Life Insurance Company.

† One local recurrence with metastasis that was controlled.

‡ Six were controlled by excision, one controlled by roentgen therapy; one with metastasis was not controlled.

TABLE II: FATE OF PATIENTS WITH RECURRENCES OF CARCINOMA OF THE LOWER LIP AFTER VARIOUS FORMS OF TREATMENT GIVEN ELSEWHERE

Form of Treatment Given to the Recurrence	Number of Patients	Eventually Presented Metastases	Died of Intercurrent Disease Before 3 Years	Well 3 Years or More	Absolute 3-Year Survival
Surgery	8	3	1	5	
Curie therapy	4	1	2	2	
Roentgen therapy	26	3	7	17	65%
None	5	4	..	..	
All cases	43	11 (25%)	10	24	56%

TABLE III: SIGNIFICANCE OF HISTOPATHOLOGIC GRADING IN THE DEVELOPMENT OF METASTASES AND IN THE PROGNOSIS FOLLOWING TREATMENT*

	Number of Patients	Eventually Presented Metastases	Incidence of Metastases	Dead of Intercurrent Disease Before 3 Years	Well 3 Years or More	3-Year Absolute Survival
Grade 1	116	11	10%	15	96	83%
	(26)	(4)	(13%)	(8)	(15)	(57%)
Grade 2	23	3	13%	6	14	59%
	(13)	(5)	(38%)	(1)	(7)	(53%)
Grade 3	3	1	33%	0	2	....
	(1)	(1)	....	(1)	..	....
Ungraded	10	0	....	0	10	....
	(3)	(1)	....	(1)	(2)	....
TOTAL	152	15	10%	21	122	80%
	(43)	(11)	(25%)	(11)	(24)	(56%)

* Figures in parentheses are for patients who came to us with recurrences following treatment of various kinds given elsewhere.

the other patients and deserves credit for most of the good results in this material.

An exclusive report of the patients treated by any one of the methods used would imply an unfair segregation of material that would also thwart our understanding of the important problem of metastases; for these reasons we have preferred to report the ensemble of our material. But there is no intent of comparison of results from different treatments, for the cases are not comparable.

In estimating the results of treatment, our difficulty is the large proportion of deaths due to intercurrent diseases that can be ascribed to the advanced age of most of

TABLE IV: RELATIONSHIP OF THE SIZE OF THE LESION TO THE DEVELOPMENT OF METASTASES AND TO THE PROGNOSIS OF PATIENTS WHO HAD RECEIVED NO PREVIOUS TREATMENT

Largest Diameter of Lesion and Form of Treatment	Number of Patients	Eventually Presented Metastasis	Incidence of Metastasis	Dead of Intercurrent Disease Before 3 Years	Well 3 Years or More Without Recurrence	Absolute 3-Year Survival
Up to 1 cm.						
Surgery	6	1		0	5	
Curie therapy	11	1	8%	2	9	83%
Roentgen therapy	20	1		2	17	
1.1 to 2 cm.						
Surgery	1	0		0	1	
Curie therapy	31	4	7%	2	28	85%
Roentgen therapy	37	1		6	31	
No treatment	1	0		...	...	
2.1 to 3 cm.						
Surgery	..	..		..	..	
Curie therapy	5	0	8%	0	4	64%
Roentgen therapy	19	2		5	12	
No treatment	1	0		..	..	
3.1 and over						
Surgery	2	1		1	1	
Curie therapy	1	0	25%	0	1	60%
Roentgen therapy	16	3		3	10	
No treatment	1	1		..	..	
All cases	152	15	10%	21	119	77%

our patients (Fig. 1). The mean age of these patients was 67 years and the normal chance of five-year survival of the group was only 76 per cent. For this reason, we present the three-year survival rate in an effort to balance the possible errors. A three-year symptom-free survival rate may be entirely satisfactory in estimating results of treatment of carcinoma of the lower lip; it is noteworthy that of 79 patients in this series that have survived between five and seven years following treatment, *not one* has presented a local recurrence or metastasis after the first three years of control.

A detailed analysis of this material will be found in the tables that accompany this paper; repetition in the text of most of the details is not warranted. The over-all three-year salvage is 80 per cent for patients who came to us without clinical evidence of metastases. The three-year survival in the group treated by roentgen therapy is 75 per cent (Table I). It is noted that curability decreases with increase in the size of the lesion and with the degree of anaplasia of the tumor; the cure rate is smaller in the group of patients that came to us with local recurrences (Table II). The three-year symptom-free survival of patients that presented metastases on admission is fair, and that of patients who presented metastases later is even better (Tables V and VI).

There were 10 local recurrences following treatment given in our hospital (1 after surgery, 1 after curie therapy, and 8 after roentgen therapy); 2 of these recurrences were accompanied by metastases. In at least 3 cases of recurrence following roentgen therapy the fact could be explained by definite errors of technic (recurrence outside of field, insufficient dose, inadequate immobilization of patient during treatments); in 3 other cases the assumed recurrences could have been an entirely different but neighboring new growth. Eight of these recurrences were ultimately controlled (7 by excision; 1 by roentgen therapy), including 1 of the 2 with metastases. Five of these 10 recurrences were in patients who presented epidermoid carcinomas Grade II. A greater incidence of undifferentiated carcinomas in the recurrent group is also found among the patients that came to us with recurrences from treatment elsewhere (Table III). A similar observation has been made by other

TABLE V: FATE OF PATIENTS WITH CARCINOMA OF THE LOWER LIP WHO PRESENTED CLINICALLY OSTENSIBLE METASTASES ON ADMISSION

Therapeutic Procedure	Number of Patients	Coincident Recurrences Following Treatment Elsewhere	Died of Intercurrent Diseases Before 3 Years	Well 3 Years or More	Absolute 3-Year Survival
Upper neck dissection following treatment of primary lesion*	8	5	3	3	37%
Palliative treatment	4	4	..	..	0%
No treatment	1	..	..	..	0%
All cases	13	9	3	3	23%

* In five instances the dissection was bilateral. There was only one operative death.

TABLE VI: FATE OF PATIENTS WITH CARCINOMA OF THE LOWER LIP WHOSE METASTASES BECAME CLINICALLY OSTENSIBLE AFTER CONTROL OF THE PRIMARY LESION

Therapeutic Procedure	Number of Patients	Average Interval Following Treatment of Primary Lesion	Died of Intercurrent Disease Before 3 Years	Well 3 Years or More	Absolute 3-Year Survival
Neck dissection	9*	7 months	2	5	55%
Palliative treatment	2†	4 months	..	0	..
No treatment	2‡	4 months	1	0	..
All cases	13**	6††	3	5	38%

* Eight upper neck dissections, one of them bilateral and one including resection of lower jaw; one radical dissection. One case with coincidental local recurrence after curie therapy was controlled. No operative mortality.

† One case with coincidental loca lrecurrence after roentgen therapy.

‡ One case was autopsy finding following death from intercurrent disease.

** In 2 cases the metastases followed control of a recurrence of the primary lesion previously treated elsewhere.

†† All but two appeared within twelve months.

authors (3), and has been erroneously attributed to dedifferentiation of carcinomas that recur. Actually the fact is simply explained by a greater tendency to recurrence among the less differentiated carcinomas.

Only a total of 16 patients (8 per cent) in this series of 195 actually died of cancer; this number includes 7 of the 13 patients who had metastasis on admission (5 of whom received no curative treatment), 3 other patients who were not treated, 5 of the 13 patients who developed metastases after treatment of the primary, and 1 who had an extensive local recurrence that was not controlled. To these 16 cases may be added 3 other cases of death from intercurrent disease during the course or immediately following treatment. These bring the total possible deaths from cancer to 19, or 10 per cent.

Only one patient has been lost to view from this series, and that after he had been followed for three years: this is a credit to our Social Service Department and to the zeal of its director, Mrs. Miriam Hoag. With few exceptions the patients were followed at intervals of one to three months during the first two years and twice, or at least once, yearly thereafter. Patients are weighed at every clinic visit and any important loss in body weight is investigated, as are all complaints that may be due to another cancerous growth. Even when there are no spontaneous complaints the patients are often questioned for gastrointestinal and other symptoms. Visiting frequently at our hospital, these patients are familiar with the more serious condition of other patients and the importance of early diagnosis. In 2 patients, a malignant tumor of the intestines was diagnosed and treated in our hospital: one died of heart disease after an abdominoperineal resection for cancer of the rectum, and the other is living with recurrence following resection

for mesothelioma of the ileum. Four other patients have died of internal cancer that was diagnosed in the terminal stages.

CONCLUSIONS

1. Roentgen therapy is the treatment of choice in most cases of carcinoma of the lower lip.

2. Adequate irradiation capable of controlling the disease and assuring the best esthetic results requires a balance of the treatment factors in accordance with the extent and character of the primary lesion.

3. The size of the lesion, the degree of differentiation of the tumor and previous unsuccessful treatments all have an important bearing on the incidence of metastases and on the prognosis following treatment.

4. Metastatic adenopathies from carcinoma of the lower lip are best treated by a supra-omohyoid neck dissection, often bilateral; a larger intervention may be necessary in a few cases only.

5. A prophylactic neck dissection in cases of carcinoma of the lower lip is not justified as a routine procedure.

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SUMARIO

Roentgenoterapia del Carcinoma del Labio Inferior

De mayo, 1940, a diciembre, 1944, 195 enfermos con carcinoma del labio inferior fueron enviados al Hospital Estatal Ellis Fischel para Cáncer (Misuri). La mayoría presentaban carcinomas bien diferenciados. Cuarenta y tres tenían recidivas locales consecutivas a varias formas de tratamiento en otras partes. Ocho no podían recibir ningún tratamiento curativo; 17 recibieron tratamiento quirúrgico; a 52 con lesiones pequeñas o moderadas se les administró curieterapia superficial, y los 118 restantes recibieron roentgenterapia.

Debido a la edad avanzada de los enfermos (promediando 67 años) y la consiguiente disminución de la expectativa de vida, se dan los índices de sobrevivencias de tres años más bien que los resultados de cinco años. Justifica esto además el hecho de que, de 79 enfermos de la serie que sobrevivieron de cinco a siete años el tratamiento, ninguno presentó recidiva local o metástasis más allá de los primeros tres años.

Para los enfermos recibidos para tratamiento sin signos de metástasis, el índice global de sobrevivencias de tres años llegó a 80 por ciento; para los que recibieron (116) la roentgenterapia, a 75 por ciento.

La mayor parte de los enfermos fueron tratados con 110 kv., pero para las lesiones que afectan más de la mitad del labio, las que se extienden a la mucosa bucal o la mandíbula, y en las recidivas difusas consecutivas a un tratamiento inadecuado, es preferible usar 200 a 250 kv. Las lesiones pequeñas pueden tratarse en ocho a diez días con excelente resultado. En las mayores, resultó más satisfactorio alargar más el tratamiento, hasta un máximo de seis semanas. La dosis total varía de 3,000 a 7,000 r, medidos al aire en la superficie del labio.

Llegóse a las siguientes conclusiones:

(1) La roentgenterapia representa el tratamiento de elección para la major parte de los casos de carcinoma del labio inferior.

(2) Una irradiación adecuada para destruir el tumor y obtener el mejor resultado estético exige el equilibrio de los factores terapéuticos de conformidad con la extensión y naturaleza de la lesión primaria.

(3) El tamaño de la lesión, el grado de diferenciación del tumor, y los fracasos de los tratamientos anteriores, todos estos factores, guardan una importante relación con la incidencia de metástasis y con el pronóstico posterapéutico.

(4) La invasión metastática de los ganglios linfáticos por el carcinoma del labio inferior se trata mejor con una disección supraomohioidea del cuello, a menudo bilateral; sólo en algunos casos puede ser necesaria una intervención más extensa.

(5) En los casos de carcinoma del labio inferior, no está justificada, como procedimiento sistemático, una disección profiláctica del cuello.

Cancer of the Larynx

Five-Year Results of Radiotherapy[1]

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THE PURPOSE OF this report is to discuss the indications and limitations of radiotherapy in cancer of the larynx and to analyze the extent to which these and other results call for a revision of opinion on the present treatment of this disease. This paper is based upon a study of 107 consecutive, microscopically proved cancers of the larynx treated by radiation in the Chicago Tumor Institute from the time it opened in April 1938 through December 1942,[2] with a minimum observation period of five years.

The controversy regarding the best treatment for laryngeal cancer revolves about two questions:

1. Is radiotherapy or surgery preferable for early true cord lesions suitable for laryngofissure?
2. Is radiotherapy or surgery preferable for operable laryngeal cancer suitable for laryngectomy?

The main difficulty in attempting to answer these questions is due to the following circumstances: (*a*) Curability of early lesions of the vocal cord by laryngofissure is between 80 and 85 per cent and the curability of more advanced but operable cancer of the larynx by laryngectomy has increased to about 60 per cent. Surgeons understandably hesitate to substitute a newer method for an older and more established procedure until adequate evidence is available. (*b*) Whereas surgical technic for laryngeal cancer has become more or less standardized, the development of the principles and technic of irradiation is in mid-progress. As the technic improves, the curability increases, a fact that has not received adequate attention in the literature quoting comparative results of the two methods. (*c*) One obvious difficulty is that, generally speaking, the radiotherapist occupies himself largely with the treatment of cancer discarded by the surgeon and thus has only a limited opportunity to treat early and hence favorable cases. A study of the literature elicits the significant fact that, with isolated exceptions, the largest cancer clinics throughout the world treat only 8 or 10 operable cancers of the larynx each year. Since many cases are treated surgically, it becomes clear that the accumulation of enough operable cases treated by radiotherapy is a long and difficult task; yet only in this way will it ever be possible to settle the question of the relative merits of surgery and irradiation in laryngeal cancer. In spite of these difficulties, there has accumulated during the last twenty-five years sufficient experience to permit certain conclusions and to indicate the trend toward further progress.

The first successful results of radiotherapy in laryngeal cancer were reported in 1922 by Regaud, Coutard, and Hautant before the International Congress of Otology in Paris (1). The report dealt with six advanced inoperable carcinomas treated with roentgen rays. The first large series was reported in 1932 by Coutard (2), who obtained *27 per cent five-year cures in 142 patients* treated in the Curie Institute of Paris. In 1941, Ahlbom (3) reported 76 carcinomas of the larynx treated in the Radiumhemmet in Stockholm between 1930 and 1939. Thirteen lesions were limited to the vocal cords, and all were cured either by laryngofissure and post-

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[1] From the Chicago Tumor Institute. Presented at the Thirty-third Annual Meeting of the Radiological Society of North America, Boston, Mass., Nov. 30–Dec. 5, 1947. Aided by grants from the National Cancer Institute.

[2] Fifty-two patients were selected for treatment at the Institute from among those seen at the Veterans Administration Facility, Hines, Ill.

operative telecurie therapy or by telecurie therapy alone. Thirty-eight more advanced cases were treated by laryngectomy and postoperative telecurie therapy. Two-thirds of these were apparently cured after five years. In 1947, Lenz (4) reported 27 per cent cures in a series of 110 patients treated with roentgen rays in the Presbyterian Hospital, New York, between 1931 and 1941. Most of the lesions were advanced. Baclesse (5) in 1946 reported 341 carcinomas of the endolarynx treated in the Curie Institute between 1919 and 1940, his five-year curability being 17 per cent. This low figure is due to the fact that most of the lesions were very advanced—only 17 per cent were comparatively early—and also to the rigid standards of statistical analysis. The marked improvement in results in more recent years is indicated by the figures for 1940, showing 13 five-year cures out of 33 cases.

A more recent trend toward the treatment of operable lesions by radiotherapy has resulted in several reports, notably by Blady and Chamberlain (6), Lederman (10), Harris (7), and the writer. In 1944, Blady and Chamberlain reported five-year results in 36 patients, 23 of whom had intrinsic lesions. The net five-year survival for this latter group of 23 patients was 59 per cent. Kramer (8) in 1946 reported 32 early lesions of the vocal cord treated by Harris in the Mount Sinai Hospital, New York. Twenty-two of 26 patients treated three or more years prior to the report were free of disease, an 85 per cent cure rate, which the author cites as comparing favorably with the best results of laryngofissure. This high curability illustrates what can be accomplished by adequate radiotherapy in selected early lesions. In 1946 the present writer (9) reported 42 per cent five-year cures among 47 patients, 31 of whom had extrinsic inoperable lesions. The curability in the operable group was approximately 50 per cent. Lederman (10) in 1947 reported 40 cases treated with teleradium, of which 14 were free of disease after five years. Twelve out of 17 operable lesions were apparently cured.

As to results of laryngectomy, the high curability of 73.5 per cent cited by MacKenty (11) in 1929 is readily explained by the fact that in a large proportion of his cases the carcinoma was so early as to be curable either by laryngofissure or radiotherapy. The exceptionally low curability of 15 per cent quoted by such pioneer laryngologists as Gluck and Soerenssen (12) is due to the fact that they accepted for operation many cancers which others would have rejected as inoperable. In 1945, Colledge (13) reported 60 per cent cures by laryngectomy and Martin (14) 58 per cent (of 36 cases). New and Waugh (15) in 1934 reported 56.1 per cent and more recently (1947) New, Figi, *et al.* (16) reported 60.2 per cent of traced patients well five years after laryngectomy, with only 1.9 per cent hospital mortality (104 laryngectomies, 88 patients traced). As a result of important advances in preoperative and postoperative care, the mortality of laryngectomy has been reduced to such a low figure that the primary risk in patients of good physical condition need no longer contraindicate the operation.

CLASSIFICATION

It has been customary in the past to separate cancer of the larynx into two main forms: extrinsic and intrinsic. There is, however, some confusion as to the exact definition of these terms, since they are used in the literature with different meanings depending upon whether the classification is surgical or anatomical. According to the surgical classification, extrinsic carcinoma includes lesions arising in the aryepiglottic folds, piriform fossae, and post-cricoid region, as well as those arising within the laryngeal cavity which have spread outside the boundaries of the larynx. This classification found its justification in that extrinsic carcinomas by definition have been considered as being beyond surgical approach, whereas the intrinsic lesions are considered operable. The anatomic classification refers to the primary site of origin of a lesion regardless of its subsequent extension. Thus all tumors which

arise within the larynx, regardless of their extension to the pharynx, remain by definition intrinsic.

Some of the European workers, notably Leroux-Robert (17) and Baclesse in France, Ahlbom in Sweden, and Lederman in England suggest that the terms "intrinsic" and "extrinsic" be abandoned and advocate that the term "cancer of the larynx" be restricted to cancer arising within the confines of the larynx. Baclesse uses the term "cancer of the larynx" to indicate lesions of the endolarynx as distinguished from those of the hypopharynx (aryepiglottic folds and suprahyoid portion of the epiglottis). He further divides true cancer of the larynx (endolarynx) into (*a*) vestibular cancer (posterior surface of the epiglottis and ventricular band), (*b*) glottic cancer (true cord), and (*c*) subglottic cancer.

Ahlbom draws the dividing line between the larynx and hypopharynx at the laryngeal inlet, *i.e.*, the edge of the epiglottis, the aryepiglottic folds, and the arytenoid region. Any carcinoma, the greater portion of which has developed on the laryngeal or inner side of this boundary line, is called a laryngeal carcinoma; all the others are referred to as hypopharyngeal carcinomas. Ahlbom points out that carcinoma of the epiglottis is the most difficult to classify. When the lesion occupies the laryngeal surface of the epiglottis, it is classified as endolaryngeal. The other carcinomas of the epiglottis are grouped either with the hypopharynx or the vallecula and base of the tongue. Martin proposes that the borderline between extrinsic and intrinsic carcinoma of the larynx be drawn at the edge of the ventricular bands.

Lederman agrees with Leroux-Robert and Baclesse in avoiding the terms extrinsic and intrinsic. He subdivides true laryngeal cancer into: (*a*) supraglottic (ventricle, false cord, and infrahyoid epiglottis), (*b*) glottic (superior surface or free margin of true cord), and (*c*) subglottic (subglottic space), emphasizing the importance of dividing the epiglottis into supra- and infrahyoid parts because tumors of the suprahyoid epiglottis, the aryepiglottic fold and arytenoids together form an epilaryngeal group which should be regarded as pharyngeal rather than laryngeal. When the lesion is advanced, it is often impossible to distinguish between a pharyngeal or laryngeal origin, though careful clinical and radiographic studies before, during, and after irradiation help in making the distinction. Various classifications have been proposed. Baclesse suggests the following criteria:

1. The exact topographic involvement
   (*a*) Vestibular cancer (laryngeal surface of epiglottis and false cord)
   (*b*) Glottic cancer (lesions of true cord)
   (*c*) Subglottic cancer
2. The extension of the neoplasm
3. The presence of adenopathy
4. The involvement of cartilage

Nielsen and Strandberg, and more recently Lederman, have attempted to divide laryngeal cancer into stages, according to extent of disease. The latter suggests the following grouping:

Stage I: Lesion is limited to tissue of origin with no restriction of mobility.

Stage II: Lesion has crossed the mid-line or has spread to adjacent intralaryngeal tissues, but is still within the confines of the larynx.
   (*a*) Full mobility of the larynx is retained
   (*b*) Mobility of the larynx is impaired but not lost

Stage III: The tumor remains within the confines of the larynx but laryngeal fixation is present.
   (*a*) Complete hemilaryngeal fixation
   (*b*) Fixation of one side and impaired movement of the other

Stage IV: Spread has occurred outside the larynx, as shown by
   (*a*) Invasion of the laryngopharynx
   (*b*) Invasion of the pre-epiglottic space
   (*c*) Invasion of thyroid cartilage
   (*d*) Presence of cervical lymph node metastases
   (*e*) Presence of distant metastases

Certainly these efforts toward more detailed study of the origin and extent of laryngeal cancer and classification are in

the right direction, for without a uniform classification statistical comparisons of the results of treatment with different methods or in different clinics are without meaning. It is generally agreed that this aspect of the problem should be studied by a committee of an international congress.

CONCENTRATION RADIOTHERAPY

The term concentration radiotherapy was introduced by the writer (18) for convenience in emphasizing two factors: the administration of a large total dose in a relatively short period (eighteen days) and the use of an increasing dose through a diminishing portal. The principles and technic of this method have been recorded. The method of irradiation now generally used in laryngeal cancer is the divided dose technic, known as the Coutard method, or some modification of it. Roentgen treatments are given daily to two lateral fields. The treatment period varies between four and six weeks, and the total dose between 6,000 and 7,000 r. It is important to emphasize that Coutard recognized that this method fails to cure the more radioresistant carcinomas. Concentration radiotherapy is much more intense, Thus, instead of giving 6,000 to 7,000 r in four to six weeks to two fields, 6,000 to 6,500 r are given in eighteen days to one field. The total dose is sufficient to produce an "epithelite" and usually also an "epidermite." With certain exceptions, the dose is increased daily as the size of the portal is diminished. In an effort to exert a greater effect upon the more radioresistant tumors, the intensity of the treatment had to be increased. The problem, obviously, was how to increase the intensity and at the same time avoid radionecrosis.

Total Treatment Time: The available evidence seems to indicate that the more radioresistant lesions require not only a larger total dose but also as large a daily dose as the tissues of the tumor bed can tolerate, and this is the fundamental basis of concentration radiotherapy. Our experience indicates that, within certain limits, the more radioresistant the lesion is, the shorter must be the time of treatment and the larger the daily dose; thus, a superficial papillary carcinoma of the true vocal cord can be sterilized by 6,000 to 6,500 r given through two portals in thirty to forty days, but a more extensive squamous carcinoma which has infiltrated the muscles of the hemilarynx, and caused partial and sometimes complete fixation of the structures, requires a more intense irradiation. A considerable number of lesions of this type and extent, generally incurable by current technics, have been cured by 6,000 to 6,500 r given through one portal in eleven to eighteen days.

Voltage, Roentgen Intensity and Fields: Most of the patients have been treated with 400-kv. roentgen rays. A comparative study is under way to determine whether similar results can be accomplished with 200-kv. rays. The average roentgen intensity has been about 7 r per minute. Generally speaking, one portal has been used, but in special circumstances the treatments are given through two portals. With certain exceptions, the size of the field is reduced as the dose is increased. A light centering device and an adjustable diaphragm are indispensable for accurate localization. Because of the use of very small portals, the patient must be immobilized carefully and the set-up checked at intervals during the treatment.

Present Technic: The question of the optimal number of treatment days for cancer of the larynx is still a subject of study and remains unsettled. The eleven-day technic formerly employed yields excellent results in apparently unfavorable lesions but, as previously reported, it is too intense for certain patients; hence, as of July 1945, the number of treatment days was increased to eighteen. The "interval treatment" has also been highly effective in certain advanced and fixed lesions, but has proved too intense for some cases; it is therefore used only in selected cases with full knowledge of the risk of radionecrosis. The following technic, published in 1946, is currently in use:

1. For early intrinsic carcinoma of one or both true or false cords with complete or partial mobility: 400 kv.; 5 ma.; filter, 5 mm. of copper; distance, 84 to 115 cm.; single lateral port, 5 × 5 cm., gradually diminished to 3 × 3 cm.; average intensity, about 7 r per minute; two equal treatments daily for eighteen days, beginning with 100 r twice a day and increasing to 250 r twice a day; total dose, 6,000 r measured on the skin.

2. For more extensive intrinsic and for extrinsic carcinoma with or without regional cervical metastases and with partial or complete fixation: 400 kv.; 5 ma.; filter, 7 to 8 mm. of copper; distance, 75 to 80 cm.; single lateral port, 7 × 5 cm. gradually diminished to 4 × 3 cm.; average intensity, about 6 r per minute; two equal treatments for eighteen days, beginning with 85 r twice a day and increasing to 275 r twice a day; total dose, 6,500 r measured on the skin. Metastases too extensive to be included in the fields receive additional irradiation.

Radium Treatment—Telecurie Therapy: To Janeway and Quick much credit is due for pioneer work in the radium treatment of cancer of the larynx. Some striking results are recorded by Quick (19) in the Janeway Memorial Lecture delivered at the Fifth International Congress of Radiology in 1937. Subsequent interesting reports on radium treatment of cancer of the larynx include those of Harmer (20), Ahlbom (3), and Lederman (21).

The telecurie therapy apparatus[4] of the Chicago Tumor Institute contained 10 gm. of radium until September 1943, when 3 gm. were released for war purposes. The apparatus has now been restored to its original strength. The filter is 1 mm. of platinum, the target-skin distance 12.5 cm., and the portals vary from 4 × 4 cm. to 8 cm. in diameter.

The following telecurie therapy technics are in use:

(*a*) 90,000 mg. hr. to each of two lateral fields in eighteen days; field, 6 × 6 cm. reduced to 5 × 5 cm.

(*b*) 105,000 mg. hr. to the side of the lesion and 35,000 mg. hr. to the opposite side; total dose, 140,000 mg. hr. in twenty treatment days; field, 8 cm. in diameter.

(*c*) 140,000 mg. hr. to the side of the lesion in twenty treatment days; field, 8 cm. in diameter for first 105,000 mg. hr. reduced to 6 × 6 cm. for last 35,000 mg. hr.

Complications: Most patients with advanced cancer of the larynx or hypopharynx are in very poor general condition; some are so ill that they die either before or soon after irradiation is begun. A certain number die in connection with tracheotomy or gastrostomy. As a group, therefore, these patients have a poor prognosis from the very beginning. Deaths from bronchopneumonia are not uncommon as a natural consequence of the advancing disease. It is not surprising, therefore, that death occurs not infrequently at or about the height of the radiation reaction, by which it is often precipitated.

The disintegration of the tissues in the tumor bed following irradiation results in a local defect from which the patient may or may not recover. Under the most favorable conditions, the carcinoma is sterilized and recovery ensues in spite of the extent of the original lesion. In advanced and more radioresistant lesions, however, the carcinoma may be only partly sterilized. Under these circumstances, and when the patient survives the irradiation, the treatment is followed by varying periods of improvement, with ultimate recurrence and death. These are the palliative results of radiotherapy. When the lesion is uncontrolled and the local and general conditions are too unfavorable, the patient fails to show an initial improvement, continues to lose ground, and dies soon after the irradiation, generally of bronchopneumonia with uncontrolled disease. In still another group with advanced disease the lesion is sterilized in spite of its extent, but the patient succumbs soon after treatment and the autopsy shows no sign of the original cancer. In this group it seems that the

[4] Grateful acknowledgement is made to the Union Minière du Haut Katanga for making available the 10-gm. radium bomb.

TABLE I: FIVE-YEAR RESULTS OF RADIOTHERAPY IN RELATION TO EXTENT OF CARCINOMA AND MOBILITY OF LARYNGEAL STRUCTURES

Stage of Carcinoma	Total No. of Patients Treated	Well	1938 Treated	Well	1939 Treated	Well	1940 Treated	Well	1941 Treated	Well	1942 Treated	Well
Cords movable or partly fixed	37	22	5	2	5	3	4	3	14	7	9	7
Cords fixed; advanced cancer; regional metastasis	70	15	10	2	6	1	9	2	25	5	20	5
TOTAL	107	37										

Note: Seven patients died from other causes than cancer (without recurrence) less than five years after treatment, leaving 37 five-year cures in 100 cases, or 37 per cent (35 per cent if the indeterminate cases are not deducted). Of the 7 patients who died from other causes than cancer (except for one case of cerebral metastasis), 2 died of perforated gastric ulcer, 1 one year and the other three years and five months after treatment; 3 of coronary disease, 1 one year and seven months, 1 three years and four months, and 1 three years and eight months after treatment; 1 from cerebral hemorrhage, two years after treatment; 1 from cerebral metastasis, four years and four months after treatment.

Since publication of these cases in 1946, 5 patients have died from other causes than cancer (without recurrence) more than five years after treatment (five and a half, six, six, seven, and seven years) and are listed as cured. One died with probable recurrence four years after treatment and is counted as lost, and one counted as lost in our 1946 report has been found, free of cancer.

destruction of an advanced lesion left a defect so extensive and in such relation to vital structures that it could not be repaired in time to prevent such fatal complications as infection or hemorrhage or both. Undoubtedly the poor general condition of the patient is a crucial factor in these deaths. Finally, an extensive carcinoma of the larynx may be sterilized but the advanced stage of the disease, poor general condition of the patient, and the intensity of the irradiation result in radionecrosis. Laryngectomy has been performed in some of these cases and the microscopic examination has confirmed the absence of cancer. A number of these patients have survived.

Although these complications are more likely to occur after intense irradiation, they may follow moderate irradiation. Conversely, debilitated patients with advanced disease sometimes tolerate very intensive irradiation and escape these complications. Intensity of irradiation is, therefore, not the sole factor and perhaps not the principal one. The writer believes, in agreement with Ahlbom and others, that the histologic structure of the tumor, the condition of the tumor bed, the presence or absence of infection, the gross character of the tumor (as regards its papillary or infiltrating character), and the general condition of the patient are some of the known factors that have an important influence on these complications. It is generally agreed that without or even with an autopsy, it is often difficult to determine whether a given death is due to a complication produced by the cancer itself or by the radiation.

In this series two patients died as a direct result of radionecrosis. The treatment in both was too intense in the light of present knowledge. In seven other fatal cases varying degrees of necrosis were present, but the general condition of all the patients was so poor and the lesions were so advanced that these factors alone were sufficient to account for the deaths, although the final outcome was probably precipitated by the irradiation. In a small group, varying degrees of radionecrosis developed, followed by healing. In several laryngectomies performed for suspected recurrences, examination of the larynx failed to disclose any sign of carcinoma, but only necrosis of laryngeal tissues with marked secondary infection.

Results: Although our conclusions are based entirely on five-year results, it is interesting to note the significance of three-year results of radiotherapy in cancer of the larynx. The fact that out of 43 three-year cures reported in 1946 only one recur-

TABLE II: FIVE-YEAR RESULTS OF RADIOTHERAPY IN RELATION TO OPERABILITY AND SURGICAL INDICATIONS*

Stage of Carcinoma and Surgical Indications	Total No. of Patients Treated	Well	1938 Treated	1938 Well	1939 Treated	1939 Well	1940 Treated	1940 Well	1941 Treated	1941 Well	1942 Treated	1942 Well
Extrinsic, inoperable	67	14	11	2	5	1	9	2	23	3	19	6
Intrinsic, suitable for laryngectomy	25	13	3	2	4	1	1	1	11	6	6	3
Intrinsic, suitable for laryngofissure	15	10	1	0	2	2	3	2	5	3	4	3
TOTAL	107	37										

* See note, Table I.

rence developed after the third year is interesting and coincides with observations of other workers. In 1946 the writer reported that out of 52 patients who died of uncontrolled disease following irradiation between 1938 and 1942, inclusive, 88 per cent died within two years and 98 per cent within three years. In Lenz's series of 87 cases, 90 per cent of deaths from cancer occurred within three years of treatment. It is interesting that the incidence of recurrence during the fourth and fifth years is one in forty-three, or about 2 per cent.

Table I shows that out of 37 patients with movable or partly fixed cord lesions, 22 were free of disease after five years. Out of 70 advanced cases in which the cords were completely fixed, in some cases with metastasis to regional lymph nodes, 15 were free of disease after five years.

Table II shows that among 15 patients with lesions amenable to laryngofissure, 10 were free of disease more than five years; 3 died of other causes without recurrence. Of 25 patients with lesions amenable to laryngectomy, 13 remained well more than five years, and of 67 advanced and inoperable lesions, 14 were cured.

The 107 cases recorded in Tables I and II represent all the cases treated between April 1, 1938, and Dec. 31, 1942. This same group was reported in 1946[3] with a minimum observation period of three years. It is now reported with a minimum observation period of five years.

Of the 43 patients reported in 1946 as living and apparently well, the following can be stated: Five died, apparently free from cancer, of other causes, five and a half, six, six, seven, and seven years after treatment. One died four years after treatment with probable recurrence and one patient who had been lost track of and therefore counted as lost has been found, free of disease. Consequently, out of 43 patients reported to be living and well two years ago, only one had a subsequent recurrence (four years after treatment). The three-year "cures" reported two years ago, therefore, remain the same for the five-year period.

CRITERIA FOR SELECTION OF TREATMENT

For the individual case of operable intrinsic carcinoma of the larynx, the choice between laryngectomy and radiotherapy may be difficult. The selection of treatment is highly individual, and no strict rules can be applied to all cases. There is obviously a need for both methods if all patients are to receive the best treatment. The following criteria are suggested as a guide in choosing between surgery and radiotherapy:

General Considerations: The patient s age and general condition, his life expectancy, and the presence or absence of serious organic disease are important factors which influence the decision.

Extent of the Lesion: Lesions which are extrinsic by origin or extension are generally regarded as inoperable, and the pres-

[3] In the report of 1946, the number of cases, totalling 118, included 11 not confirmed by biopsy, though there was no doubt about the clinical diagnosis. In the present report these are omitted, reducing the total number to 107. The apparent discrepancy between the 43 patients reported as "well" in 1946 and the present figure of 37 is due to the fact that 6 patients in whom the diagnosis was not confirmed by biopsy included in the 1946 report are excluded in the present report.

ence of cervical lymph node metastasis usually indicates inoperability. When the lesion is so advanced as to be inoperable and apparently incurable by radiotherapy, irradiation should be designed with the view to palliation.

Site of Origin: Lesions arising in the ventricle, false cords, or base of the epiglottis are generally more radiosensitive, whereas subglottic lesions are usually more radioresistant. The radiosensitivity of lesions of the true cord depends largely on the extent and degree of infiltration.

The Microscopic Structure: Many surgeons and pathologists believe that the more undifferentiated carcinomas have a worse surgical prognosis and some clinicians are influenced by the histologic grade of the biopsy specimen in their choice of treatment. Personal experience indicates that it is hazardous to draw conclusions from the histologic structure of a biopsy specimen except in a general way. Actually it is not safe, on this basis, to express a dogmatic opinion that the lesion is of high or low malignancy or that it is radioresistant or radiosensitive. To this general statement there are two exceptions: When the microscopic structure shows marked anaplasia, especially with the formation of spindle cells, the lesion is nearly always highly malignant and offers an unfavorable prognosis regardless of whether surgery or irradiation is used. The other exception is when the epithelial cells are uniformly small and transitional in type, especially when they show a convoluted plexiform arrangement. In such lesions one often finds interspersed islands of differentiated squamous elements with a tendency toward pearl formation. Cancers of this latter type are generally radiosensitive and, when not too advanced, are curable by adequate irradiation. This structure is usually found in lesions originating in the false cords, the ventricles, the aryepiglottic folds, and the epiglottis. The term "transitional-cell carcinoma" is often used to describe such cancers. Histologic grading when done by a pathologist especially experienced and skilled in this field has a value, but can be hazardous unless interpreted broadly and in the light of the results of effective irradiation.

The view that squamous carcinoma is radioresistant has become entrenched in the literature. Every effort should be made to correct this fallacy, which is based on two errors. One is the belief that squamous carcinoma is resistant to irradiation; the fact is that it is sensitive to adequate radiotherapy. The other error lies in dependence upon a single biopsy specimen as giving a reliable histologic picture of the lesion, whereas there may be—and frequently are—other areas in the same tumor that are undifferentiated.

Mobility of Laryngeal Structures in Relation to Radiosensitivity and Radiocurability: The gross character of the lesion influences its radiosensitivity and radiocurability. Generally speaking, papillary lesions are radiosensitive; infiltrating lesions, relatively radioresistant. Mobility of the laryngeal structures generally indicates that the lesion is early or, if more advanced, that it is papillary and not infiltrating. From the point of view of irradiation, such a lesion is radiosensitive and to a considerable degree radiocurable, the curability being directly related to the extent of involvement, the degree of malignancy, the general condition of the patient, and the efficiency of the treatment.

Partial or complete fixation is often due to inflammation caused by secondary infection and not to carcinomatous invasion. Such fixation occurs especially after one or more biopsies. It generally begins to diminish and disappears soon after irradiation is begun, and in cases of doubt this response is a useful sign in interpreting the cause of the fixation. Rapid increase in mobility also occurs after a small amount of irradiation when the lesion is highly radiosensitive. From a practical point of view, the early and rapid response is an indication of radiosensitivity and probable radiocurability.

No sharp line of demarcation can be drawn between radiosensitive and radioresistant lesions. The quality of radio-

sensitivity varies in degree, and there is no accurate method of expressing the variation. This fact makes it exceedingly difficult to evaluate new methods of treatment, and the critical observer who effects a startling result with a new method of irradiation is haunted by the possibility that the result may have been due more to high radiosensitivity than to the special method employed.

GENERAL COMMENT

Before 1922 surgery constituted the only form of treatment for laryngeal cancer. During the last twenty-five years the effectiveness of radiotherapy has improved to a degree that its use in properly selected operable lesions is now generally accepted. Two main problems arise in connection with treatment: (1) the choice between surgery and radiotherapy for early carcinoma of the true cord amenable to laryngofissure and (2) the choice between laryngectomy and radiotherapy for operable laryngeal cancer beyond the scope of laryngofissure.

Regarding the first, laryngofissure is a well established procedure yielding 80 to 85 per cent cures in carefully selected cases of cancer of the vocal cord. The results of radiotherapy in this group are at least as good as surgery with the advantage that, generally, the voice after radiotherapy is better (Baclesse, Ahlbom, Lederman, Lenz, Harris, Kramer, and Cutler). Laryngofissure yields the best results in lesions limited to the middle or anterior two-thirds of one cord with complete mobility. Once the disease involves the posterior extremity of the cord, crosses the mid-line, extends subglottically, involves the false cord or becomes partly fixed, it is no longer suitable for laryngofissure. If the histologic structure, as indicated by the biopsy, shows a highly malignant anaplastic carcinoma (Grade IV, Broders), most laryngologists consider laryngofissure inadequate.

Laryngofissure has a long record of favorable results and should not be abandoned. At the same time adequate recognition must be given to the increasing evidence that radiotherapy yields equally good results with a better voice, and the patient should be allowed to choose the treatment he prefers. If laryngofissure is used, one should choose the case carefully, excluding lesions which are not strictly limited. Recurrences following laryngofissure do not respond as well to radiotherapy as does the original lesion. Colledge (13) warns against exploratory laryngofissure on the grounds that if the incision cuts through tumor tissue, the best technic for the radical operation is thereby made impossible.

Regarding the choice between laryngectomy and radiotherapy, the choice is simple when the patient's age or general condition contraindicates radical surgery, when the lesion is otherwise clearly inoperable, or when the patient refuses laryngectomy; otherwise the choice may be very difficult. The natural reluctance of the patient to lose his larynx merely increases the responsibility of the surgeon and radiotherapist.

It has been stated that early cord lesions suitable for laryngofissure constitute the best target for radiotherapy and that radiotherapy is a much more efficient substitute for laryngofissure than for laryngectomy. This is only partly true. A much more important contribution of radiotherapy than as a substitute for laryngofissure is in the group of lesions beyond the scope of laryngofissure, in which laryngectomy is the only other alternative. *Lesions unsuitable for laryngofissure by virtue of site, extent, or histologic structure, but still not completely fixed by carcinomatous invasion, are ideally suited for radiotherapy, with a curability equal to that of laryngectomy.*

In 1931, I began to treat selected patients with operable carcinoma of the true cords by irradiation. At first, irradiation was tried only when the patient refused laryngectomy or when there were general contraindications to operation. As the results improved, lesions of borderline operability were treated, and finally, in 1938, irradiation of operable intrinsic lesions was practised by choice, provided

the laryngeal structures were not completely fixed by carcinoma.

The present procedure is to limit laryngectomy to cases of intrinsic cancer in which there is total fixation of the laryngeal structures and in which there are no local or general contraindications to surgical treatment, provided it is established that the fixation is due to carcinomatous invasion and not to inflammation. As the results of irradiation improve, the classification of operability becomes stricter. When the cords are still movable or only partly fixed, irradiation is chosen in preference to surgical removal regardless of the histologic grade or the extent of the lesion. In borderline cases, irradiation may be tried when a patient asks for a chance to be cured by this method, with the understanding that laryngectomy may still be necessary. In this connection, the radiotherapeutic test may be used; if the response is favorable, the treatment is completed. When the lesion appears to be unfavorable for radiotherapy and amenable to laryngectomy, the patient is urged to accept surgical treatment, but if he refuses, he is given irradiation with the clear understanding that the chances of success are remote and that he will still probably be faced with laryngectomy. This course is justified because it is now established that previous correct irradiation does not interfere seriously with subsequent laryngectomy.

The selection of treatment is highly individual, and no rules can be applied to all cases. The attempt to choose the best treatment for each case is guided by the following criteria: (*a*) the operability of the lesion, intrinsic or extrinsic, and the presence or the absence of metastatic involvement of cervical lymph nodes; (*b*) the general condition of the patient, his life expectancy, and the presence of serious organic disease; (*c*) the character of the lesion with respect to origin, extent, histogenesis, microscopic structure and, more particularly, the extent to which it has infiltrated and fixed the laryngeal structures; (*d*) the patient's temperament and his ability to adjust himself to laryngectomy and the extent to which his work and economic status are dependent on the normal use of the voice.

In the treatment of clearly operable cancer of the larynx, the choice between laryngofissure and irradiation is not nearly so important as the choice between laryngectomy and irradiation. When a patient is faced with loss of the larynx and use of an artificial voice, he is confronted with a serious problem. The first question that occurs to him is what chances there are of cure without laryngectomy, and the responsibility of the laryngologist and the radiologist in advising him is evident. The surgical results are generally familiar, but the more recent results of irradiation are not yet well known.

The crucial question is to what extent, if any, are the chances for a successful operation jeopardized by radiotherapy. Much of course depends on the type of irradiation. Certainly the dissection is likely to be more difficult and the healing delayed when the treatment factors have been such as to cause severe damage to the irradiated tissues. With the use of smaller fields and careful attention to all the other known factors designed to reduce radiation injury to normal tissues, the chances of complications are so reduced as to be negligible in most instances. It is becoming generally accepted that previous correct irradiation does not seriously complicate subsequent laryngectomy. This is especially true with current technics using small fields. Brunschwig has reported the results of panlaryngectomy in a group of patients with extensive recurrences after roentgen therapy and agrees with this view. Bernheimer, who has had a large experience, is of the same opinion, and our own experience supports this position.

It is interesting that, as early as 1938, Jackson and Jackson (22) stated that there are growths classed as operable for which the patient is justified in choosing irradiation in preference to operation and predicted that the future would probably

witness a progressive decrease in the relative number of laryngectomies. This prediction has proved to be correct. Since this statement was made, significant progress has been achieved in the radiotherapy of laryngeal cancer, which has been reflected in the five-year end-results published from several clinics. It is therefore startling to read recent articles and discussions on cancer of the larynx in which irradiation is mentioned casually as a palliative procedure for inoperable lesions. In view of the evidence at hand, the failure to give serious consideration to the results of modern radiotherapy is not to the best interests of the patient who is faced with the loss of his larynx.

CONCLUSIONS

Thirty-five per cent[5] five-year cures were obtained in a series of 107 consecutive unselected cases of laryngeal cancer treated by radiotherapy. More than half the cases were inoperable. Among the operable cases beyond the scope of laryngofissure whose only surgical alternative was total laryngectomy, radiotherapy effected 52 per cent five-year cures, and among the inoperable group, 20 per cent are free of disease after five years. The five-year curability among the cases in which the cords were not completely fixed is 60 per cent. Based upon these and other results, the following conclusions seem permissible.

Radiotherapy is indicated in selected cases of laryngeal cancer. When the cords are freely movable or only partly fixed by the carcinoma, curability is high (60 per cent) and radiotherapy is the method of choice. Laryngectomy is indicated for intrinsic lesions with complete fixation of the cords occurring in good surgical subjects of good life expectancy, provided the fixation is caused by carcinomatous invasion and not by inflammation. If, after careful consideration of all factors, a decision between radiotherapy and laryngectomy remains difficult, a radiotherapeutic test or complete irradiation should be considered as the initial procedure. There is every reason to expect that further improvements in the technic of irradiation and earlier diagnosis will further diminish the necessity for total laryngectomy.

[5] The seven patients who died before five years of causes other than cancer are counted as having died of cancer.

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SUMARIO

Cáncer Laríngeo. Resultados de Cinco Años de Radioterapia

En una serie de 107 casos consecutivos sin seleccionar de cáncer laríngeo tratados con la radioterapia, obtuviéronse curaciones de cinco años en 35 por ciento (contando como muertes de cáncer las de siete enfermos que murieron antes de cinco años de otras causas que cáncer). Más de la mitad de los casos eran inoperables. Entre los casos operables más allá del alcance de la laringofixión cuya única alternativa era la laringectomía total, la radioterapia efectuó 52 por ciento de curaciones de cinco años, y entre los inoperables, 20 por ciento se hallan exentos de la enfermedad al cabo de cinco años. La curabilidad de cinco años entre los casos en que las cuerdas no estaban completamente fijas es de 60 por ciento. A base de estos y de otros resultados, las siguientes conclusiones parecen justificadas.

La radioterapia está indicada en casos seleccionados de cáncer de la laringe. Cuando las cuerdas se mueven sin dificultad o sólo se hallan parcialmente fijadas por el carcinoma, la curabilidad es alta (60 por ciento) y la radioterapia es el método de elección. La laringectomía está indicada en las lesiones intrínsecas con fijación total de las cuerdas en buenos sujetos quirúrgicos de buena expectativa de vida, con tal que la fijación se deba a invasión carcinomatosa y no a inflamación. Si, tras el cuidadoso estudio de todos los factores, sigue siendo dificil decidir entre la radioterapia y la laringectomía, hay que considerar como procedimiento inicial una prueba terapéutica o la irradiación total. Existen excelentes motivos para esperar que nuevos perfeccionamientos de la técnica irradiatoria y el diagnóstico más temprano reducirán todavía más la necesidad de la laringectomía total.

La técnica preferida por el A. es la introducida por él mismo con la designación de "radioterapia de concentración." Las características esenciales consisten en la administración de una dosis total grande en un período de tiempo relativamente breve (18 días) y en el empleo de una dosis creciente a través de una puerta cada vez menor.

(Discussion of the papers by del Regato and Cutler will be published with a paper on Carcinoma of the Larynx by Harris in RADIOLOGY *for November)*

Werner's Syndrome

A Case Report[1]

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THE PAST generation has witnessed a revolutionary change in our conception of bone function. Considered originally an inert framework for the anchorage or support of viscera, or a part of the blood-forming system, the skeleton is now known to be a functioning organ of vital importance in the metabolism of the body. As our understanding of the role of the osseous system unfolded, the education and training of the roentgenologist broadened so that he became familiar with the general diseases which are reflected in bones.

Few phases of the field of clinical medicine have been left unexplored by the progressive roentgenologist. Imperceptibly his role has changed and he has become as thoroughly versed in medical, as his predecessor was in surgical, radiography.

Clear evidence of the changing status of the roentgenologist is his familiarity with the radiographic appearances of the deficiency states and of the constitutional disorders which leave their imprint on the osseous system. Especially in the field of orthopedics he must be thoroughly familiar with the bodily conditions which are accompanied by skeletal changes, since patients with orthopedic complaints suffer some constitutional diseases in which the orthopedic manifestations are inconsequential.

Illustrative of the foregoing is the rare condition to be reported here—Werner's syndrome—which was recently studied at the Hospital for Joint Diseases and which was correctly identified from the roentgenograms.

CASE REPORT

L. K., a white, unmarried female, aged 35, visited the clinic on June 5, 1947, complaining of a chronic ulcer of the right foot. After preliminary examination, she was admitted to the hospital for lumbar sympathetic block in the expectation of healing the ulcer.

Fig. 1. Senile appearance of the patient. The face is small and triangular in shape. The eyelashes and eyebrows are scant. The skin about the eyes, mouth, and chin is atrophic and wrinkled. There is a slight bilateral proptosis.

The patient's mother died at 50 years of diabetes and a heart condition. The father was alive and well but also suffering from diabetes. Two brothers were alive and well. The patient had poliomyelitis when nine months old, followed by weakness of hips, for which she was placed in a cast. At the age of three, she was able to walk again but was left with an everted right foot which was corrected at the age of eleven at a local hospital. She was able to wear ordinary shoes until 18 years of age but callosities developed which compelled her to pur-

[1] From the Department of Radiology, Hospital for Joint Diseases, New York, N. Y. Read by title at the Thirty-third Annual Meeting of the Radiological Society of North America, Boston, Mass., Nov. 30–Dec. 5, 1947.

Fig. 2. Large indurated ulcer over the external malleolus which failed to heal despite intensive treatment.

chase special shoes. At the age of 23, the patient lost her mother. She felt her loss keenly and in the succeeding three months she lost 25 pounds, which she had never regained, so that her weight on admission was 77 pounds. At the age of 24, she experienced difficulty in vision and the diagnosis of "cataract" was made. Bilateral cataract extraction was performed four years later. No further ocular disturbances occurred until the age of 34 years, when she injured her right eye, which had since been subject to recurring inflammation, for which treatment was still being received.

The patient had the usual diseases of childhood. Following her mother's death, sugar was found in the urine, but it disappeared without treatment. A transient glycosuria occurred a few weeks prior to admission to the hospital but disappeared in one week. There was no dysmenorrhea but menstruation was extremely irregular, periods being skipped for two or three months. On admission she had amenorrhea. She had experienced occasional attacks of numbness in right hand and tongue, during which time she was unable to speak. She suffered occasional severe right temporal headaches.

Five months before admission, an ulcer developed on the left heel and shortly thereafter another appeared over the external malleolus. The first ulcer healed slowly but that over the malleolus persisted. It was for this latter condition that treatment was sought.

Physical Examination: The patient was a short, thin, poorly developed woman who appeared much older than her given age. She showed little subcutaneous fat and there was a striking disproportion between her thin extremities, pendulous abdomen, and well developed chest. All bony prominences were visible. The head was small and triangular in shape, the nose was beaked, and the face had a "bird-like" appearance. The jaw was narrow and pointed (Fig. 1). The patient wore a wig, which concealed her gray hair, and her eyelashes, eyebrows, pubic and axillary hairs were scant. The skin about the mouth, chin, and eyes was wrinkled and somewhat atrophic; over the lower extremities it was tight and glistening. There was bilateral proptosis and the conjunctiva of the right eye was injected. Opacities of the cornea and the scars of the previous operation were visible. The pupils reacted to light and accommodation. Laryngoscopic examination revealed normal movement of the vocal cords and epiglottis but several prominent superficial veins were seen in the middle third of the

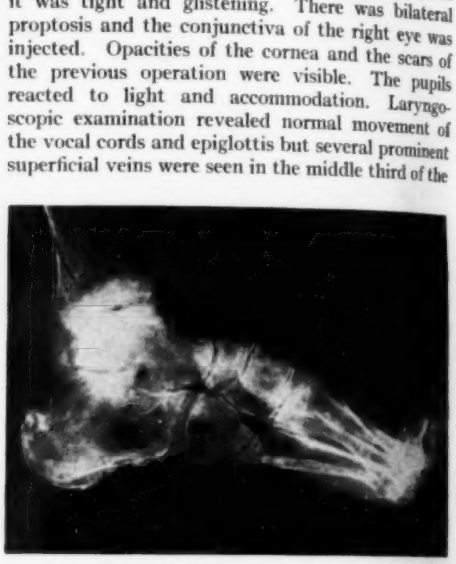

Fig. 3. Lateral view of the foot showing extreme osteoporosis. Note calcifications about the Achilles' tendon and in front of the ankle joint. The calcification of the vessels, although striking in the roentgenograms, is barely visible above the head of the astragalus in the reproduction.

cords, more notable on the left side, similar to an angioma. The thyroid isthmus was palpable and the veins about it were slightly distended. The breasts were infantile in size. Heart and lungs were apparently normal. The blood pressure was 170/80. The liver was palpable a finger's breadth below the costal margin.

There was some wasting of the muscles of the upper extremities, without loss of power. While there was also extreme atrophy of the muscles of the lower extremities, it was more noticeable below the knees. Apparently there were no muscle fibers left below the knee joints, because of the absence of motion in the ankle joints and feet. The feet were fixed in equinovarus position. The ankle reflexes were apparently absent, but there were no sensory disturbances. The history was questionable owing to the fact that it was difficult to reconcile the fixed contractures with the statement regarding poliomyelitis. There was a large indurated ulcer over the lateral malleolus of the left foot and several keratotic callus-like lesions were present on the feet (Fig. 2). There was no evidence of scleroderma.

Laboratory Data: Throughout the patient's stay at the hospital, the sugar content of the urine varied from 0.5 to 4.0 per cent. Blood sugar over a considerable period of time varied from 150 to 246 mg.

The sugar tolerance curve showed an extreme diabetic response. Other findings were: alkaline phosphatase, 3.9 units; inorganic phosphate, 3.4 mg.; cholesterol, 461 mg.; calcium, 10.3 mg.; sedimentation rate, slightly elevated; basal metabolic rate, plus 10. Serologic and hematologic examinations proved negative.

Radiographic Examination: There was an extreme osteoporosis of all of the bones of the lower extremities, most notable in the tibiae. The marrow cavities were expanded and the cortices thinned.

Fig. 4. Extreme osteoporosis of the bones of the hand and thinning of the cortex of the intermediate phalanx of the fourth finger. There are irregular calcifications in the soft tissues at the tips of the fourth and fifth fingers and at the metacarpo-phalangeal joints. Note calcification of the vessel adjacent to the first metacarpal bone.

The transverse trabeculae seemed to have completely disappeared. The periosteum was not thickened. All the vessels of the extremities showed an advanced calcification of the Mönckeberg variety. Flocculent calcifications were seen in the soft tissues, in the bursae, and in the tendinous attachments of the knees, ankle joints, and feet. In no instance was there any calcification of articular cartilage. The feet were small, and both showed hammer-toe deformities. In some areas, as in the distal portions of the fifth metatarsal bones, there was a fine granular thinning of the cortex (Fig. 3).

Fig. 5. Lateral view of the skull showing advanced hyperostosis frontalis interna and normal denture. The disharmony between the patient's age and the skeletal and dental age as revealed by the roentgenograms, furnished the clues upon which the roentgen diagnosis was predicated.

In the upper extremities, the osteoporosis was most manifest in the phalanges. Although the cortex in the majority of the bones was intact, it appeared to be thinned in some. Irregular calcareous deposits were seen, particularly in the soft tissues of the elbow joints posteriorly, more especially on the right side, and apparently in the triceps tendon as well as in the soft tissues around all of the small joints of the hands. Some of these appeared to be within the capsules and others in the ligaments and tendon sheaths. Deposits were seen likewise in the subdeltoid bursae. The periarticular tissues of the proximal interphalangeal joints appeared to be thickened (Fig. 4).

The examination of the heart and lungs proved to be negative. Radiographs of the spine showed an advanced osteoarthritis with no calcification of the ligaments or intervertebral cartilages. The lateral view of the lumbar spine revealed an extensive calcification of the abdominal aorta of a degree seen only in advanced life.

It was the lateral view of the skull (Fig. 5) which furnished a clue to the etiology of the condition. The sella turcica was small. The pineal body was not visualized. An advanced hyperostosis frontalis interna was seen and all the teeth appeared to be remarkably well preserved. It was difficult to reconcile the evidence of senility in the extremity

bones and blood vessels with such normal denture. There was obviously disharmony between the skeletal and the dental age. While the changes in the extremities momentarily suggested hyperparathyroidism or chronic renal insufficiency with secondary hyperparathyroidism, the validity of the diagnosis could not be proved by the thickened cranial bones and the intact peridontal membranes of the teeth. It was obvious, therefore, that we were dealing with a condition characterized by the skeletal changes of premature senility and calcification. This impression was strengthened by an awareness that the patient was thirty-five years of age. The diagnosis of Werner's syndrome was therefore made from the roentgenograms and established clinically.

Course: During her stay at the hospital, the patient's diabetes remained uninfluenced by any dosage of regular protamin or globulin insulin. Thyroid extract was administered without benefit. The ulcer on the foot did not heal despite continuous furacin dressings, left paravertebral sympathetic block, and bed rest. Skin grafting was considered, but the patient left the institution against advice.

Comment: It is obviously beyond the scope of this report to review in detail the literature relating to the disease in question. A few notes will suffice. The syndrome was originally described by Otto Werner (1) in 1904, in his doctor's thesis from the Ophthalmological Clinic of Kiel, under the title "Cataract in Connection with Scleroderma." All four of his patients were members of the same family. The first report in American medical literature was that of Oppenheimer and Kugel (2), who renamed the disease "Werner's syndrome," described three cases, and furnished autopsy data. Two of the patients were brothers. One of the best discussions of the subject, with an extensive bibliography, is that of Thannhauser (3), who reviewed the literature up to 1945 and reported five additional cases. The distinguishing characteristics of the syndrome, according to Thannhauser, are: (1) shortness of stature and characteristic habitus; (2) premature graying of the hair; (3) premature baldness; (4) scleropoikiloderma; (5) trophic ulcers of the legs; (6) juvenile cataracts; (7) hypogonadism; (8) tendency to diabetes; (9) calcification of the blood vessels; (10) osteoporosis; (11) metastatic calcification; (12) familial tendency.

It is obvious that the condition which we have described fulfills the aforesaid criteria, with one exception. We were unable to establish any familial tendency, although it may be significant that the mother died at the age of fifty and that both the mother and father suffered from diabetes.

NOTE: The author wishes to acknowledge his indebtedness to Dr. Martin Vorhaus and Dr. Theodore Fox for their co-operation in the clinical investigation of this case.

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SUMARIO

Síndrome de Werner. Observación

Señálase la importancia que reviste para el radiólogo el conocimiento perfecto de los estados orgánicos que van acompañados de patología ósea. Esto lo demuestra bien un caso del raro síndrome de Werner, que describiera por primera vez en 1904 el autor mencionado, con el titulo de "Catarata en conexión con Esclerodermia."

El caso descrito ahora reveló las siguientes características del síndrome: (1) talla baja y típico físico; (2) canicie prematura; (3) calvicie prematura; (4) escleropoiquiloderma; (5) ulceras tróficas de las piernas; (6) cataratas juveniles; (7) hipogonadismo; (8) tendencia diabética; (9) calcificación de los vasos sanguíneos; (10) osteoporosis; y (11) metástasis calcáreas.

El diagnóstico se hizo roentgenográficamente y se confirmó clínicamente.

Radioactive Iodine: Its Use as a Tool in Studying Thyroid Physiology[1]

RULON W. RAWSON, M.D.,[2] and BENGT N. SKANSE, M.L.[3]

In 1915, MARINE and his associates (1–3) demonstrated that the thyroid is capable of concentrating iodine to an approximate level of 5,000 times that of the blood. This unique function has provided students of biology and medicine with a valuable means for studying the physiology of the thyroid. In recent years the physicists have provided dynamic tools, in the radioactive isotopes of iodine, with which certain functions of the thyroid can be investigated at physiologic levels never before obtained.

Though several radioactive isotopes of iodine have been described, only three have been widely used in studies of thyroid function. The earliest studies with radioactive iodine were done with I^{128}, an isotope having a half-life of only twenty-five minutes, which limited the time of study. This isotope is prepared by slow neutron bombardment of iodine. Iodine^{130}, the twelve-hour half-life isotope, has been used in biological studies and in treating certain cases of Graves' disease. This isotope is a product of the cyclotron and is prepared by bombarding metallic tellurium with deuterons. Iodine^{131} is likewise prepared in the cyclotron by deuteron bombardment of tellurium, but has also been formed by the bombardment of tellurium with slow neutrons which have their source in the chain-reacting pile. The eight-day half-life of this isotope has made it a particularly convenient tool in physiologic studies of the thyroid.

The earliest reported studies of thyroid physiology with radioactive iodine were those of Hertz, Roberts, and Evans (4). In their studies with isotopes, these investigators repeated some of the classic studies reported by Marine and noted the unique avidity of the thyroid for iodine. Subsequently they observed that thyroids made hyperplastic by the administration of thyroid-stimulating hormone, or by the ingestion of cabbage, concentrated a greater percentage of the administered iodine than did their controls. Leblond and Sue (5) also observed that the thyroid has an affinity for iodine which is increased after treatment with thyrotropic hormone and is greatly decreased following hypophysectomy.

Chaikoff and his associates (6) observed that thyroids of hypophysectomized rats concentrate less iodine than do those of control animals and that such thyroids are capable of converting the collected iodine to diiodotyrosine. During the twenty-six-hour period that they followed their animals, practically none of the administered labeled iodine was demonstrated in the thyroxin fraction. This same group of investigators have observed that the thyroids of guinea-pigs previously treated with thyroid-stimulating hormone not only have an increased avidity for iodine but that they secrete it into the blood stream as a radioactive iodine thyroxine at a much greater rate than do the thyroids of untreated controls.

Keating, Rawson, Peacock, and Evans (7) have used radioactive iodine in comparing the anatomical changes of the thyroid with changes in iodine metabolism produced upon administration of the thyroid-stimulating hormone. In one study

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[1] From the Thyroid Clinic and Research Laboratory of the Massachusetts General Hospital and from Harvard Medical School, Boston, Mass. Presented at the Thirty-third Annual Meeting of the Radiological Society of North America, Boston, Mass., Nov. 30–Dec. 5, 1947.

[2] Assistant Professor of Medicine, Harvard Medical School, and Associate Physician, Massachusetts General Hospital. Present address, Memorial Hospital, New York.

[3] Henry P. Walcott Fellow in Medicine, Harvard Medical School.

TABLE I: EFFECT OF VARYING DOSES OF THYROTROPIC HORMONE ON COLLECTION OF RADIOACTIVE IODINE, MEAN ACINAR CELL HEIGHT, AND WEIGHT OF THYROID GLAND

Thyrotropic Hormone (Units per Day)	Animals	Mean Cell Height (microns)	Animals	Thyroid Weight (mg.)	Animals	Collection of Radioactive Iodine (per cent of injected dose)
0 (Controls)	5	1.9 ± 0.1*	5	3.3 ± 0.4*	9	8.2 ± 3.4*
1/8	4	4.4 ± 0.1	4	8.3 ± 1.1	9	35.3 ± 2.4
1/4	4	5.8 ± 0.1	4	11.4 ± 1.4	9	43.5 ± 2.9
1/2	5	6.9 ± 0.1	5	12.8 ± 0.8	7	43.8 ± 2.0
1	5	7.9 ± 0.2	5	17.7 ± 4.2	9	40.8 ± 3.0

* The mean of each group is given with the standard error of the mean.

of the effect of varying doses of thyrotropic hormone (1/8, 1/4, 1/2, and 1 unit), there was a continued increase in thyroid weights with increasing dosage, but the mean acinar cell heights reached a maximum with the smaller doses, beyond which little increase was observed. The avidity for iodine was found to increase sharply with the smaller doses of thyroid-stimulating hormone, but no greater increase was observed where the daily dose of hormone exceeded 1/4 of a unit. The average mean cell height, thyroid weight, and iodine collection for each experimental group is recorded in Table I.

The same investigators determined the effects of repeated doses of thyrotropic hormone in animals injected with one unit of thyroid-stimulating hormone daily. Beginning with the first dose, animals from the treated and from a control group were sacrificed twenty-four hours after each injection. It was observed that the mean acinar cell heights increased rapidly after the initial dose, and by successively smaller increments following each subsequent dose. The weight of the thyroid on the other hand increased slowly at first, but later precipitously. No increase was noted in the collection of iodine in the first twenty-four-hour period, the maximum increase in avidity for iodine being observed between forty-eight and seventy-two hours (see Table II).

In a third experiment, the effect of the thyroid-stimulating hormone on the loss of stored iodine was studied. Starved cockerels, forty-eight-hours old, were given 0.5 microgram of iodine labeled with radioactive iodine. Treated animals received one unit of thyroid-stimulating hormone each day for three days, one group of chicks being sacrificed twenty-four hours after each injection. Controls were sacrificed on the first and third days. During the first twenty-four-hour period a loss of 75 per cent of the stored iodine was observed and during the three-day period of treatment, a total loss of 96 per cent, as compared to a loss of 49 per cent in the untreated controls (see Table III).

From these studies, it would appear that the first changes to occur as the result of treatment with thyroid-stimulating hormone are hypertrophy of the thyroid cell and a loss of thyroid iodine, probably as an hormonal iodine. Though the thyroid weight increases slightly during the early period of treatment with thyrotropic hormone, the precipitous increase in the weight of the gland is not evident until seventy-two hours after administration of the first dose. It is important, however, to point out that an increased avidity for iodine is not manifest until twenty-four hours and is maximum only forty-eight hours after the maximum loss of iodine has been demonstrated. This might suggest that the increased collection of iodine is dependent upon a previous purging of the thyroid's hormonal iodine rather than upon any specific function of the thyroid-stimulating hormone.

At the clinical level, radioactive iodine has proved very instructive in the study of the pathologic physiology of various types of thyroid disease. Hamilton and Soley (8) were the first investigators to report the use of radioactive isotopes in tracing the course of iodine given to human beings.

TABLE II: EFFECT OF REPEATED DOSES OF THYROTROPIC HORMONE ON COLLECTION OF RADIOACTIVE IODINE, MEAN ACINAR CELL HEIGHT AND WEIGHT OF THYROID GLAND

Time after Initial Dose (hours)	Animals	Mean Cell Height (microns)	Animals	Thyroid Weight (mg.)	Animals	Collection of Radioactive Iodine (per cent of injected dose)
0 (Controls)	8	1.8 ± 0.1*	5	3.0 ± 0.3*	12	6.0 ± 1.8*
24	9	4.9 ± 0.1	5	5.0 ± 0.3	27	8.2 ± 0.9
48	8	5.9 ± 0.1	5	8.1 ± 0.4	26	20.8 ± 2.6
72	8	7.4 ± 0.2	5	17.5 ± 1.6	18	42.0 ± 3.0
96	10	8.4 ± 0.1	5	19.9 ± 3.2	33	49.5 ± 2.2
120	8	9.3 ± 0.2	5	33.4 ± 2.7	17	50.9 ± 4.6
Additional Controls						
24	..	.....	.	.....	16	7.7 ± 1.4
48	..	.....	.	.....	18	9.2 ± 1.0
72	..	.....	..	.....	8	7.4 ± 3.4
96	..	.....	..	.....	27	8.1 ± 1.3
120	6	1.9 ± 0.1	5	3.3 ± 0.4	19	10.3 ± 1.4

* The mean of each group is given with the standard error of the mean.

They compared the uptake of labeled iodine by the thyroids of normal controls with that of patients with various thyroid diseases. The determinations were made by placing a Geiger counter over the isthmus of the thyroid gland and measuring the gamma rays emitted from the radioactive iodine that had collected in the thyroid. They also studied the urinary and fecal excretion of the administered radioactive iodine over a period of five days. It was observed that iodine given orally was absorbed rapidly from the gastro-intestinal tract and that it was demonstrable in the thyroid within twenty minutes of the time of ingestion. A negligible amount was excreted in the feces. It was also observed that normal individuals, during a five-day period, had a urinary excretion of 80 per cent of the administered dose. In the first twenty-four-hour period 50 to 60 per cent was excreted. Two myxedematous patients excreted, during the five-day period of observation, 89 to 91 per cent of the administered iodine. These patients excreted only 45 to 50 per cent of the labeled dose during the first twenty-four-hour period. Thyrotoxic patients previously treated with iodine excreted about the same percentage of the administered iodine as did normal individuals. The same was true of one untreated thyrotoxic patient. It must be pointed out, however, that these investigators gave 14 mg. of iodine, as carrier iodine, an amount which is in the therapeutic range.

TABLE III: EFFECT OF THYROTROPIC HORMONE ON THE RATE OF LOSS OF RADIOACTIVE IODINE PREVIOUSLY COLLECTED BY THE THYROID

Time after Initial Dose (hours)	Animals	Percentage of Injected Dose Present	Percentage of Loss Following Thyrotropic Hormone
0 (Controls)	10	17.20 ± 4.00*	0
24	10	4.00 ± 1.80	77
48	10	1.20 ± 0.25	93
72	10	0.70 ± 0.22	96
72 (Controls)	10	8.80 ± 2.60	49

* The mean of each group is given with the standard error of the mean.

In another study Hamilton, Soley *et. al.* (9) observed that hypothyroid children without goiters collected very little iodine. In 2 hypothyroid children with large goiters relatively larger amounts were collected in the thyroid. These thyroids, on biopsy, showed marked hyperplasia.

Hertz, Roberts, and Salter (10) used radioactive iodine in studying the iodine metabolism of patients with Graves' dis-

ease. They administered labeled iodine to thyrotoxic patients and determined the uptake of iodine by direct *in situ* measurements and by determination of the urinary excretion of radioactive iodine. The surgically removed thyroids were hydrolized in alkali and fractionated, according to the method of Harington, being separated into diiodotyrosine and thyroxine-like fractions. Patients having untreated Graves' disease were found to excrete between 10 and 37 per cent of the administered iodine if the dose of carrier iodine were small. Analysis of the thyroxine-like and non-thyroxine-like fractions of the excised thyroid showed a general trend of the labeled iodine to be increasingly in the thyroxine-like fraction as the time following administration of the iodine increased.

Keating, Power, Berkson, and Haines (11) followed the rate at which radioactive iodine is excreted in various states of thyroid function. They observed that normal subjects excrete an average of 65 per cent of the dose in the urine and that the rate of excretion levels off between twenty-four and thirty-six hours after administration of the iodine. Myxedematous subjects were observed to excrete between 85 and 90 per cent of the iodine but the rate of excretion was much slower than in the normal. In hyperthyroidism it was found that the excretion was much less than in normals and that the rate leveled off much more quickly.

In a study of the urinary excretion of radioiodine in various thyroid conditions, Skanse (12) has observed that euthyroid individuals, when given a dose of 100 micrograms of sodium iodide labeled with 100 microcuries of I^{131}, excrete, in a forty-eight-hour period, between 53 and 84 per cent, with an average of 66 per cent of the tracer. Patients having Graves' disease, when given such tracers, excrete between 6 and 32 per cent and an average of 19 per cent of the administered iodine. Six patients having untreated myxedema excreted between 72 and 92 per cent of a similar tracer of iodine, but at a much slower rate than normal individuals.

The urinary excretion of radioiodine by patients having untreated Graves' disease, we have found to be so characteristic as to justify its use as a diagnostic test in patients suspected of having this disease. In two instances of thyrotoxicosis factitia, where the patients were taking thyroid surreptitiously in doses adequate to cause elevated basal metabolic rates and blood iodine, the diagnosis was suggested by the observation that practically all of the administered tracers were excreted. It is of interest that patients who have recently had priodax for x-ray visualization of the gallbladder excrete most of the radioiodine given within an indefinite period of time following cholecystography.

Studies with radioactive iodine have been very instructive in studying certain aspects of thyroid tumors. Hamilton, Soley, and Eichorn (13) were the first investigators to use radioiodine for comparing the iodine-concentrating capacity of thyroid cancers with that of normal thyroid tissue. With autoradiographic technics, they observed that practically no iodine is deposited in cancerous tissue and that iodine collected by the surrounding normal thyroid tissue is deposited in the colloid. Frantz, Ball, Keston, and Palmer (14) studied three patients having distant metastases from cancer of the thyroid. They observed that in one of these patients, only one metastasis, of the adenoma malignum type, collected an appreciable amount of iodine.

Marinelli, Foote, Hill, and Hocker (15) with autoradiographic technics demonstrated that so-called "benign metastasizing struma" and certain follicular adenocarcinomas collect significant amounts of iodine. They concluded that pick-up of iodine is closely linked with certain structural qualities, which include orderly cell arrangement in a follicular pattern and the presence of colloid-like material.

Seidlin, Marinelli, and Oshry (16) have had the rare opportunity of studying a patient with hyperthyroidism arising from a widely metastasizing hyperfunctioning cancer of the thyroid. Radioiodine ad-

ministered to this patient was retained by all of the known metastases in concentrations great enough to warrant its administration in therapeutic amounts. Subjective and objective improvement followed intensive therapy with radioactive iodine in this case.

In our clinic we have used radioiodine technics, *i.e.*, autoradiograms and direct measurements of tissue digests, in comparing the iodine-collecting function of benign tumors of the thyroid with the degree of differentiation shown by such tumors on histologic examination. The same technics have been used in comparing the function of certain cancers of the thyroid with that of the surrounding uninvolved tissue.

The benign tumors in general we have found to possess some capacity to concentrate radioactive iodine, but usually less than that possessed by normal thyroid tissue. Almost parallel to the grades of differentiation, there has been observed a spectrum of gradually increasing affinity for iodine, with the more differentiated tumors concentrating greater amounts of the labeled iodine. At the functional end of the spectrum were a few tumors which concentrated more iodine than did the uninvolved tissue. These tumors showed a uniform hypertrophy in contrast to a picture of hyperinvolution observed in the surrounding uninvolved tissue.

In our series of thyroid cancers a measurable pick-up of iodine by the tumor tissue was observed in 10 out of 21 cases. Avidity for iodine by the tumors which did collect iodine was extremely low when compared to the iodine-collecting capacity of normal thyroid tissue. The ratios were as high as 1:13, and as low as 1:60. These observations are not encouraging to one interested in treating cancer of the thyroid with radioactive iodine.

One of the most interesting studies in which the writers have been involved is the determination of the effect of removal of the normal thyroid on the iodine-collecting function of non-functioning distant metastases from primary thyroid cancers. In a co-operative study done at the Sloan Kettering Institute in New York and at the Massachusetts General Hospital, we have been able to make observations on 14 patients having distant metastases from cancer of the thyroid which had practically no function. In these cases the thyroids were removed surgically or destroyed by large doses of radioactive iodine. In 8 of the patients there has been observed a significant increase in avidity for iodine by the metastasis. In 6 of these patients the increase has been great enough to warrant a trial of therapy with radioactive iodine.

In evaluating the many reports of studies of thyroid physiology in which so-called tracer amounts of radioactive iodine have been used, the question comes to mind, "Is the amount of radiation emitted by these isotopes great enough to alter any normal functions of the thyroid?" In our studies on rats, with thyroid weights of 5 to 20 mg., and on cockerels, with thyroid weights of 3 to 6 mg., we have used tracer doses of 1 and 2 microcuries of I^{131}. On the basis of microcuries per milligram of tissue, we calculate that we are using amounts of radioactivity within the range of therapeutic doses given by Chapman and Evans in treating Graves' disease. They have found the effective administered dose of twelve-hour iodine to be between 0.8 and 1.0 millicuries per estimated gram of thyroid tissue and of the eight-day iodine to be between 0.20 and 0.22 millicuries per estimated gram of tissue.

During the past eighteen months, in our laboratory, we have been concentrating a great deal of effort in evaluating the effect of radioactive iodine on certain well known functions of the thyroid. It has been observed, by Skanse, that in the cockerel collected doses of 1 and 5 microcuries of I^{131} will interfere with the growth and iodine-collecting capacities of thyroid tissue as measured at sixteen and twenty-four days following administration of the isotope. At the twenty-four-day interval it has been observed that there occurs a definite impairment of the action of thyroid-stimulating hormone. From these studies, which are now in progress, it would

appear that certain so-called tracer doses cannot be administered without altering the normal physiologic pattern of the thyroid. It is important then that the minimal amount of radioactive iodine which can be administered without altering thyroid function be determined. The same is true of other isotopes. If these tracers are too small to be accurately detected with our present methods, then it will become necessary to perfect newer and more sensitive measuring equipment for carrying on such studies.

SUMMARY

We have presented a brief review of certain studies in which radioactive iodine has been used in evaluating some of the physiologic reactions of the thyroid. The need of determining the minimal amount of these and other isotopes which can be administered without impinging on normal physiology has been pointed out.

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SUMARIO

Yodo Radioactivo: Su Empleo como Instrumento para Estudiar la Fisiología Tiroidea

La concentración de yodo por el tiroides ha resultado ser un auxiliar valioso en el estudio de la fisiología de dicha glándula. Numerosos investigadores han verificado estudios de este género con yodo radioactivo. Keating, Rawson, Peacock, y Evans, por ejemplo, descubrieron experimentalmente que la administración de la hormona tirotropa provoca hipertrofia del tiroides, pérdida del yodo fijado e hiperavidez hacia el yodo administrado. Los estudios clínicos indican que el yodo administrado oralmente es absorbido con rapidez en el tubo gastrointestinal, encontrándose en el tiroides en término de 20 minutos de la ingestión. Se ha demostrado que la excreción urinaria de yodo radioactivo varía en diversos estados tiroideos. En la enfermedad de Graves no tratada, la excreción de yodo ha resultado

ser tan típica que justifica su empleo como prueba diagnóstica en los enfermos en que se sospecha la presencia del mal.

Los estudios con yodo radioactivo han resultado en particular útiles para ciertas fases de los tumores tiroideos. Los benignos en general, según han observado los AA., poseen alguna capacidad para concentrar el yodo radioactivo, pero habitualmente menor que la del tejido tiroideo normal. En una serie de cánceres tiroideos, observóse una absorción mensurable de yodo por el tejido neoplásico en 10 de 21 casos, pero sumamente baja, comparada con la capacidad yodoabsorbente del tiroides normal. Entre 14 enfermos con metástasis remotas no funcionantes de cáncer tiroideo, la tiroidectomía o destrucción de la glándula con grandes dosis de radioyodo fué seguida en 8 casos de una avidez significativa hacia el yodo de parte de las metástasis. En 6 dicho aumento fué suficiente para justificar una prueba terapéutica del yodo radioactivo.

Recapitulando, señálase que la experimentación denota que ciertos estudios "indicadores" con radioyodo pueden ir seguidos de alteraciones de la fisiología normal del tiroides. Recálcase la importancia de determinar las dosis mínimas de isotopos que pueden administrarse sin afectar la fisiología normal.

Radioactive Iodine Studies of Functional Thyroid Carcinoma[1]

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THE HISTORY OF THE recognition of functional thyroid carcinoma goes back less than a century. The first pertinent recorded observation was roughly eighty years ago, when Müller (1) noted that a metastatic lesion in bone was strikingly similar to normal thyroid tissue. Approximately fifty years ago von Eiselsberg (2) described a case of thyroid cancer in which, following total thyroidectomy, hormonal balance was maintained by the activity of a destructive growing cancer involving the sternum. Five years ago we (3) reported the first case of metastatic thyroid carcinoma to be shown, by Geiger counter and radioautograph, to take up radioactive iodine. In a more detailed account, we later (4) reviewed briefly these studies and others of the last twenty years, including the historic paper published in 1940 by Hamilton and Soley (5), "Deposition of Radioactive Iodine in Human Thyroid Tissue." In this paper the authors presented radioautographs of two thyroid carcinomas which failed to show uptake, and they made the following statement: "The failure of cancerous thyroid tissue to acquire appreciable quantities of radioiodine, as shown in these experiments, suggests the impracticability of therapeutic application of this radioelement in malignancies of the thyroid. It is possible that in other cases of carcinoma of the thyroid, radioiodine may be stored in the affected tissue in quantities sufficient for treatment." The first sentence has been quoted extensively but little credit has been given to the authors for the second. The failure of uptake is not surprising in view of the histologic appearance of the lesions as shown in the photomicrographs. In our series, only one case in three of thyroid carcinoma has been even a possibility for I^{131} therapy.

Cancer of the thyroid is, fortunately, a very rare form of malignant disease. Only a few physicians appreciate the fact that there are different histological and biological forms. The fulminating cases are the dramatic ones that are remembered. No doctor can forget a patient who dies with asphyxia or hemorrhage from local cancer six months after the first symptom, despite desperate surgical and radiotherapeutic measures. The pathologist also remembers the appearance under the microscope of this highly invasive anaplastic cancer with no resemblance to thyroid tissue. In addition, however, the pathologist has, to his sorrow, another memory. That memory is of his error in diagnosis. He interprets an encapsulated tumor, easily shelled out from the surrounding normal gland, as a simple adenoma. Years later bone metastases give the lie to the original diagnosis. It is this lesion which one might expect to consist of functional thyroid tissue which could take up iodine, and our first case was one in which metastases became clinically apparent seven years after removal of an "adenoma" and fourteen years after the tumor was first noticed. The failure of our therapy in this case with I^{130} and I^{131}, in spite of uptake in some of the bone lesions, was amply explained by the necropsy findings. The neoplasm showed wide variation in histological pattern, but the high uptake in those metastatic foci which were shown at postmortem to consist of well differentiated tissue encouraged us to continue the study. Our series is still disappointingly small in view of our early good fortune in securing a suitable case, and we were fur-

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ther hampered in earlier studies by the scarcity and high cost of the isotope. This presentation is in the nature of a preliminary report on our work with I^{131}, but a somewhat more detailed account of our experience with thyroid carcinoma in general.

In the evaluation of any new agent proposed for therapy in cancer, it is essential to scrutinize with care the success and failure of more traditional methods. Although at the Columbia-Presbyterian Medical Center there has been since 1925 a special Thyroid Clinic in which internists, surgeons, radiologists, psychiatrists, ophthalmologists, and surgical pathologists collaborate in the study and care of patients, no detailed account of our experience in thyroid cancer has yet been published. Patients with thyroid carcinoma constitute a very small number of those attending the clinic, but there are now enough cases with possible five-year survival to warrant reviewing them, realizing however that, except in the highly malignant form of thyroid cancer, it is hazardous to evaluate therapy unless one also knows at least the ten-year follow-up. This we now have in a considerable number of cases.

INCIDENCE

From our own hospital population, which has not been derived from an endemic goiter district, in a twenty-year period, 1924–44, we had, as accessions in the Surgical Pathology Laboratory 4,707 thyroid specimens. Table I shows these cases

TABLE I: INCIDENCE OF MALIGNANCY IN THYROIDECTOMIES, 1924–44

Toxic diffuse goiter	1,678
Toxic nodular goiter and adenoma	753
Non-toxic nodular goiter and adenoma	2,125
Carcinoma	151
Primary, 118	
Lateral aberrant, 33	
	4,707

Carcinoma: 6.6 per cent of non-toxic cases

broken down according to the diagnosis made in the laboratory. The coincidence of thyrotoxicosis and carcinoma of the thyroid is so rare as to be negligible statistically. If, then, we exclude the toxic cases in attempting to determine the relative incidence of carcinoma in the series, it will be seen that between 6 and 7 per cent of surgical specimens of enlarged glands—excluding the enlargement due to thyroiditis—are interpreted by the pathologist as showing carcinoma. There is no way of determining accurately the clinical incidence of malignancy relative to the *single nodule*. When the gland is exposed at operation, the surgeon is not infrequently surprised by his obvious error in interpretation of the physical examination. The pathologist, also, not infrequently finds it difficult to make the differential diagnosis between adenoma and non-toxic nodular goiter with areas of adenomatous hyperplasia. The incidence of *true neoplasm*, therefore, and the incidence of *malignancy* in true neoplasms vary according to the prejudices and experience of the pathologist making the diagnosis. In a ten-year period in our series, when the term "adenoma" was reserved for what was considered a true neoplasm, 21 per cent of all cases of neoplasms were considered malignant histologically.

PATHOLOGY

Various elaborate classifications of thyroid carcinoma have been proposed. They are largely descriptive, based on cell structure and architecture. More recently efforts have been made to correlate histological pattern with prognosis. If possible, the surgical pathologist should be able to differentiate between those cancers whose life span—and unfortunately that of the patient—is limited to a few months after apparent onset of disease, and those which take twenty-five years or more before finally destroying the host. It should also be emphasized that the term "benign metastasizing colloid goiter" came into use because the primary focus in the thyroid gland was missed either on physical examination or at autopsy. Wherever *complete* examination of the thyroid gland is made in a case with multiple bone metastases, at least a microscopic focus of cancer

is found if the whole gland is examined. As far as surgical specimens are concerned, this has been done only very recently, when, as will be discussed further, elective total thyroidectomy is performed to facilitate I^{131} treatment of metastatic foci.

In addition to the histopathology, there are certain gross characteristics which we feel should also be taken into account in estimating degrees of malignancy. Accordingly we have used a simple classification as our working basis, hoping that with more experience we would be able to recognize the nature of the lesions with more assurance. There are cases in which the dominant disease is in the lateral neck. These, whatever the interpretation of the origin of the lateral chain of nodules, constitute a rather special clinical group. We have, therefore, as has already been reported (6) separated the lateral aberrant thyroid (or the "so-called lateral aberrant thyroid") neoplasms from those where the main disease presents in the gland itself. In addition to this gross distinction which concerns lateral neck involvement, the encapsulated nodule, the calcified nodule (usually a rim of calcification around a papillary tumor), and the multicentric foci (often of papillary tumor also), as opposed to the hard destructive lesion with extensive local invasion beyond the capsule, are all factors to be taken into consideration. Histologically we divide thyroid cancer into three grades, which is tantamount to saying that we can differentiate between the highly malignant forms and the relatively benign forms. The intermediate group, Grade II, contains those tumors whose nature we do not recognize from the histological appearance, and whose future we are too ignorant to predict. Needless to say, we are helped in our interpretation of the less familiar histological types by the clinical history and the extent of local disease found at operation. Hindsight, because of follow-up, is also obviously a factor in such evaluation.

Up to June 1, 1947, we had a total of 139 cases of carcinoma which we considered primary in the thyroid gland. Table II shows how these have been interpreted as to grade of malignancy. It will be seen that, happily, the slower growing and perhaps later metastasizing lesions constitute nearly three-quarters of the total.

TABLE II: CARCINOMA OF THYROID. 139 PRIMARY CASES*

Grade	No. of Cases	Percentage
I	103	74.0
II	16	11.5
III	20	14.3

* To June 1, 1947.

It is with this 74 per cent that we are particularly concerned in therapy, and this group breaks down further into two distinct histological and biological types, the predominantly papillary and the predominantly adenomatous or follicular. With the aid of I^{131} studies, further breakdown is possible, as will be seen in Table III. Although there are unfortunately exceptions in behavior, and some neoplasms in which the types seem to be mixed, the behavior of the two main divisions of Grade I cancer is as distinct as their histological appearance. The papillary lesions tend to be multiple, with multiple foci in the thyroid gland (and in the lateral neck), to invade locally, to metastasize to lymph nodes and to lungs, but not to bone. On the other hand, the adenomatous or follicular cancers often appear histologically benign and the metastases resemble so much the parent tissue that, as has been said before, it was once thought that normal thyroid could metastasize and that the term "benign metastasizing colloid goiter" (8), was an acceptable interpretation of the findings. These "malignant adenoma" cancers are usually single,

TABLE III: GRADE I CARCINOMAS, HISTOLOGICAL ANALYSIS*

Type	No. of Cases	Percentage
Adenoma Malignum Functional, 49 (35.2%) Hürthle cell. 9	58	41.7
Papillary	45	32.3
	103	74.0

* To June 1, 1947.

TABLE IV: CARCINOMA OF THYROID, RESULTS, 5 to 17 Years*

Grade	No. of Cases	Lost	No Evidence of Disease	Persistent Disease	Dead
I: Adenoma malignum	46	3	23	5	15
Papillary	34	2	19	6	7
Total, Grade I	80	5	42	11	22
II	16	0	2	0	14
III	12	0	0	0	12
TOTAL	108	5	44	11	48

* To June 1, 1947.

encapsulated lesions, may never recur locally after surgical removal, are seeded early in the osseous system, do not spread to lymph nodes, and involve the lungs only late in the course of the disease. They may be further divided into embryonal, fetal, microfollicular, and macrofollicular types, a histological distinction which can be somewhat correlated with function. A variant of the malignant adenoma is the Hürthle-cell tumor which, although colloid follicles are sometimes formed, lined by the characteristic pale eosinophilic cells with granular cytoplasm, does not appear to make thyroxin as far as I^{131} studies to date are concerned.

THERAPY

The results of therapy by traditional methods in cases broken down according to grade are shown in Table IV. These cases warrant some elaboration, particularly those with long follow-up. A few such life histories are sometimes more informative than larger numbers of short-term observations.

Grade I. Adenoma Malignum: Further analysis of the 15 deaths in this group of well differentiated, potentially functional carcinomas shows that one was a post-operative mortality and one was due to intercurrent disease. Thirteen were the result of thyroid carcinoma. These deaths occurred as follows:

Seven patients died of distant metastases, sixteen, fourteen, nine, five, three, two and a half, and two years, respectively, after operation (6 of these had osseous metastases and 5 lung metastases as a terminal stage.

Four died from local disease in the neck, ten, ten, six, and five years, respectively, after operation (one of this group had lymph-node metastases, all of them being exceptions to the generalizations stated above).

Two died of local disease with mediastinal extension, each at four years.

Of those living with probable persistent disease:

One had a first recurrence eleven years after operation and now survives eighteen years after the first procedure.

One had a Hürthle-cell type of tumor recurring at eight years and is living eleven years after the first procedure.

These two cases may be "cures," but we hesitate to call them such. Three other patients survive with disease, one with local cancer only, two with bone involvement.[2] The longest duration from operation to death from disease was in a case of Hürthle-cell carcinoma previously published (Haagensen, 7), death being due to lung metastases sixteen years after operation and twenty-five years after onset.

These late deaths, sixteen, fourteen, ten, ten, and nine years after operation, show the necessity of long follow-up before attempting to evaluate grades of malignancy in thyroid carcinoma or the efficacy of any form of therapy. Of those living *without* evident disease more than five years after operation, 20 of the 23 long survivors have passed the ten-year mark, 2 being free from evidence of disease as long as sixteen years. These survivors may represent a surgical pathologist's error in interpretation or a surgeon's success in therapy, a

[2] One has since succumbed to disease.

TABLE V: THYROID CARCINOMA GRADE I. EFFECT OF PROPHYLACTIC POSTOPERATIVE RADIOTHERAPY*
(*Possible Five-Year Follow-Up, 70†*)

	Adenoma Malignum	Postoperative Radiotherapy	Papillary	Postoperative Radiotherapy
Good results	23	19	19	9
Persistent disease	5	3	6	5
Dead of disease	13‡	10‡	4	4
	41	32	29	18

* To June 1, 1947.
† Excluding 10 cases, 5 of each type, lost or dead of other disease.
‡ Of the 13 patients, 4 died of local disease and 9 with metastatic disease. Of the 10 receiving postoperative radiotherapy, 4 died of local disease and 6 of metastatic disease.

question impossible to decide without some prejudice.

Local postoperative irradiation was given to 12 of the 13 patients dead of disease; to 19 of 23 still living without disease; and to 3 of 5 with persistent local tumor. No conclusions can be drawn from these figures. More informative is the fact that in two elective total thyroidectomies recently done in preparation for I^{131} therapy (three and eight years, respectively, after excision of the original encapsulated malignant adenoma), complete study of the gland showed no persistence nor recurrence of local disease. This makes local prophylactic postoperative irradiation in this malignant adenoma group seem to have no sound logical basis unless, for some reason, it was not possible to remove the whole neoplasm or there was spillage at operation.

Grade I. Papillary Carcinoma: Further analysis of the predominantly papillary group shows that 3 died of intercurrent disease. Autopsy in 2 of these showed no persistent cancer. Four died of their thyroid carcinoma:

One five years after operation with lung metastases.
One five years after operation with local recurrence and lung metastases.
One six years after operation with local recurrence and lung metastases.
One eleven years after operation with local recurrence and lung metastases (this patient had been symptom-free for six years).

Of those living with probable persistent disease:

One had a first recurrence after ten years and now survives nineteen years after the first procedure.
One is living sixteen years after operation, twenty-six years after onset, with widespread disease. Her first local recurrence appeared five and a half years after operation and postoperative radiotherapy. There was no further local recurrence after a second excision, but nine years after the second operation there was spread to lungs, pleura, chest wall, axillary lymph nodes, mediastinum, and peritoneum.[3]

TABLE VI: THYROID CARCINOMA. FAILURES OF THERAPY*
(*Possible Five-Year Follow-up, 94†*)

Grade	No. of Cases	Dead or Persistent Disease	Per Cent Failure
I: Adenoma malignum	41	18	43.9
Papillary	29	10	34.5
II	13	11	84.6
III	11	11	100.0
	94	50	53.2

* To June 1, 1947.
† Excluding from 108 cases, 5 lost and 9 dead of other causes.

Four others survive with local recurrence twelve, seven, seven, and six years, respectively, after the first operation. All but one, a seven-year survivor, had postoperative irradiation by x-ray.

Of those *without* evidence of disease only 9 of 19 had postoperative prophylactic x-ray therapy (presumably because the surgeon found the disease less extensive or had more faith in the completeness of his operative removal). They survive as follows:

Nine, with postoperative radiotherapy, survive seventeen, eleven, eleven, ten, eight, six, six, six, and five years.
Ten, without postoperative radiotherapy, survive, 1 sixteen, 2 six, and 7 five years.

The reports of the high degree of radiosensitivity of papillary carcinoma of the thyroid are to be scrutinized carefully as to whether there was actual control of evident

[3] This patient succumbed about a month after this paper was read.

persisting neoplasm or merely long survival following a combination of surgery and x-ray therapy. Our own series is too small to evaluate the efficacy of radiotherapy in this papillary type of thyroid carcinoma. We have the impression that most cases are not highly radiosensitive, but in any extensive local lesion or in a case where the surgeon has failed to remove all of the tumor we advocate postoperative irradiation.[4] A summary of the results in relation to radiotherapy in all Grade I tumors is shown in Table V.

Grade II: Of 16 patients with Grade II neoplasms, 2 died postoperatively, one of shock and one of asphyxia, both poor risks because of the extent of their disease. One died later of intercurrent disease. Of the 13 remaining patients, 2 survive, sixteen and fifteen years, respectively, after operation, both having had postoperative x-ray therapy. In one the tumor histologically was a mixed-cell type with spindle-cell metaplasia; the other was partly papillary. Both were sizable lesions with blood vessel invasion.

Grade III: The 12 patients with Grade III lesions are all dead of disease except one, who died six days after operation, of a streptococcus infection of the finger (before the days of chemotherapy).

The figures analyzed in the preceding paragraphs are recapitulated in Table VI.

LATERAL ABERRANT THYROIDS

The cases involving the lateral neck, some of which we have previously reported (6), we choose to segregate because they seem to constitute a special biological group and particularly because they pose a special problem in possible I^{131} therapy. Table VII summarizes these cases. It will be seen that there are 6 cases of disease in the lateral neck which we have considered benign lesions. Twenty-eight of 42 malignant tumors have a possible five-year follow-up. Eleven patients of this group are dead, 9 of their disease and 2 of intercurrent disease but with no certainty of local arrest. Further analysis according to histological grade is of interest.

TABLE VII: LATERAL ABERRANT THYROID DISEASE*

	No. of Cases	Deaths
Benign	6	0
Carcinoma		
Grade I	33	7
Adenoma malignum 6	3	
Papillary 27	4	
Grade II	7	3
Grade III	2	1
	48	11

* To June 1, 1947.

Grade I. Adenoma Malignum, Aberrant (6 Cases): Five of 6 cases had a possible five-year follow-up:

One died at eight years with spine and lung involvement without local recurrence.
Two died of intercurrent disease at five and eight years, respectively, and had local persisting disease which was not progressive.

Of those living:

One survives seventeen years after the first of four successive operations during the first eleven years.
One is alive ten years after operation and postoperative irradiation, without local recurrence.[5]
One who has not quite reached the five-year mark is in good general condition, with disseminated osseous metastases of at least five years duration.

Grade I. Papillary Carcinoma, Aberrant (28 Cases): The papillary carcinomas predominate in the lateral neck. Among the 28 cases there were 4 deaths as follows:

Three died of local disease sixteen, seven, and five months after operation.
One died with local disease, brain and lung metastases nine years after operation.

Grade II: Two deaths from Grade II carcinoma were at four years from local disease and at eighteen years from local recurrence and widespread metastases.

Grade III: Of 2 patients with carcinoma classified as grade III, *one* died in less than six months with a huge local recurrence.

[4] A few earlier cases were treated by radium implantation or radium collar. Obviously, the group is too small to break down further in differential evaluation of radiotherapy.

[5] Patient has since died. Limited autopsy findings reported as showing metastases in liver.

Fig. 1. Case 1, Table XI. First recorded human radioautograph of functional thyroid metastasis, Jan. 18, 1942. Film (right) enclosed in cardboard holder (left) applied to posterior aspect of thigh over the zone of maximum uptake as shown by Geiger counter. Outline of enclosing cardboard flaps is shown near the bottom of the illustration, presumably because of scatter radiation of low intensity. The darkening of the photographic emulsion is seen. On this examination with 10 millicuries of mainly I^{130}, only about 6 per cent of the material was taken up by the remnant of thyroid gland, and 30 per cent of the administered dose by the metastasis in the right femur.

TABLE VIII: YOUTHFUL CASES OF LATERAL ABERRANT THYROID DISEASE*

Age of Onset	Age at Operation	Grade	Bilateral Neck	Thyroid Involved	X-Ray Treatment	Follow-up in Years After Operation: No Evidence of Disease	Follow-up in Years After Operation: Persistent Disease
4	4	II	+	+	+	..	11 (Local)
8	15	II	..	+	+	5	.....
10	16	Adenoma malignum	..	+	0	14	.....
14	16	Papillary	..	+	0	..	5 (Local)
16	17	Papillary	..	+	0	8	.....
18	26	Papillary	..	+	+	9	.....
21	23	III	..	0	+	8	.....
22	22	Papillary	+	+	+	..	9 (? Lungs)
22	24	Papillary	+	+	0	7	.....
23	25	Papillary	..	0	0	5	.....

* To June 1, 1947.

The survivor is living without evidence of disease ten years after operation, x-ray therapy, and a second operation for recurrence. This neoplasm histologically has always been suspect, and consultants have questioned its thyroid origin. We believe, however, that there are a few definite colloid follicles in an otherwise undifferentiated tumor.

The mortality has been high in the cases of lateral aberrant thyroid carcinoma except in one particular group, made up of young patients. There is a striking incidence of this particular form of the disease in the young. Table VIII shows 10 cases with possible five-year follow-up. The age of onset ranges from four to twenty-three years—3 in childhood, 3 in adolescence,

and 4 in young adult life. We have 7 additional cases with onset of disease before the age of twenty-five which have not yet reached the five-year mark, and I^{131} studies in this group are reported below. Youth, the striking involvement of the lateral neck, and the long survival of these patients segregate them from the rest of the cases no matter what the interpretation of the nodules in the neck, *i.e.*, as multiple foci of cancer in aberrant thyroid rests or as lymph node metastases.

I^{131} STUDIES

The first case studied here (4), and already reported as a failure of therapy, has been outlined earlier in this paper (Fig. 1).

Our second case is that of the four-year-old child with long survival, listed in Table VIII. This case has also been twice published, but before I^{131} study and therapy (6, 8). It was only because of I^{131} studies that persistent disease was recognized, although it had been suspected on clinical grounds. This child had a total thyroidectomy and bilateral neck dissection, in stages, for carcinoma of the thyroid and lateral aberrant thyroid, together with lymph node metastases. These procedures took place in July 1936 and were followed by radiotherapy. The neoplasm histologically showed some differentiation into colloid follicles but was for the most part less differentiated—solid masses of cells showing spindle-cell metaplasia. Thyroid extract was necessary to maintain hormonal balance until the child was eight years old. It was then discontinued and not until three years later was it appreciated that thyroid function was probably being maintained by a focus of neoplasm. A tracer dose of I^{131}, given by Dr. Albert Keston in February 1943, showed a focus below the angle of the right mandible. Two small nodules were palpable here and, because of the uptake, were surgically removed. They proved to be lymph nodes. In May 1943 the child was therefore given a therapeutic dose, approximately 10 millicuries, mainly eight-day isotope. With this larger dose, a Geiger counter showed no functional thyroid tissue at the site of the original thyroid gland nor substernally (where it was postulated that there might be some median aberrant gland), but a probable focus calculated to be in the right pharyngeal wall. This was confirmed by radioautograph with film exposed on body surface. This focus was again confirmed by a tracer dose six months later, but more of this dose was excreted than previously and suggested less storage in the tissue. There was no striking clinical change, however, but by August 1944 the basal rate had dropped to −30 and thyroid extract therapy was reinstituted. In December 1945, thyroid extract was withdrawn, and eleven days later a tracer dose of 300 microcuries was administered. In twenty-four hours 71 per cent of this dose was excreted. This was a higher excretion than at the last examination, indicating that there was even less functional thyroid present than previously. The pharyngeal wall focus still showed uptake, however, and at this time a small focus was also demonstrated in the mid-line in the submaxillary region. The parents were unwilling that any larger dose be given, but even this small tracer may have been effective, because a year later, after withdrawal of the hormone for ten days, a tracer of 1,200 microcuries was given and 92 per cent of the dose was excreted in the first twenty-four hours, much the highest excretion to date, indicating the presence of very little functioning thyroid tissue—an "athyreotic excretion pattern." The amount of radioactive iodine remaining in the patient was so small as to make counting difficult, but the submental and pharyngeal wall foci were still demonstrable. The child is now fifteen and a half, is taking one grain of thyroid extract daily, and has progressed normally in mental and physical development. This is very nearly twelve years after her original surgical therapy. We would like to believe that the radioactive iodine therapy has contributed to the arrest of disease, but there is no proof of this.

It was this case which gave us the idea that effective I^{131} therapy of metastases

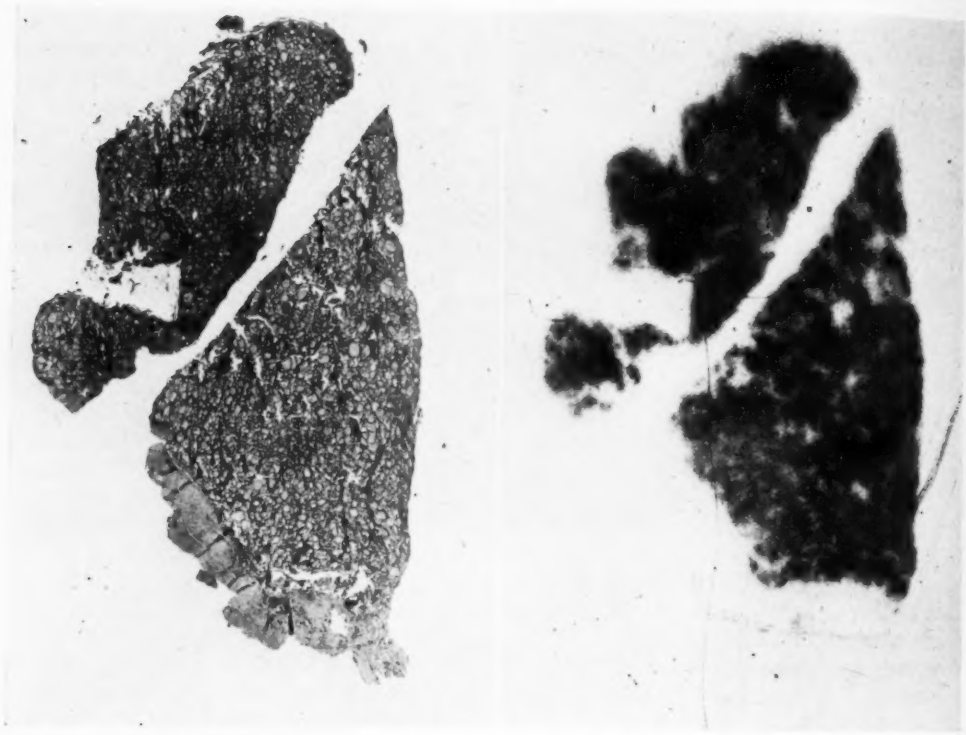

Fig. 2. Case 2, Table XI. Radioautograph of normal thyroid. Histologic preparation separate from autograph.

might well depend on the removal of the functional thyroid gland, and encouraged us to advise our first elective total thyroidectomy. The presence of normal thyroid tissue may well have accounted for failure of uptake in some, at least, of the lesions in patients with osseous metastases studied with small tracer doses.

Our third patient, a white woman, aged 49, had widespread bony metastases, and in all but one shown radiologically there was uptake of radioactive iodine, demonstrated by Geiger counter, and, in several sites, by radioautograph. This patient was highly intelligent and well aware of the nature of her disease, having already had, in addition to a partial thyroidectomy, a palliative disarticulation of her left arm at the shoulder. She knew the therapy was experimental and was willing to submit to any procedure within reason. It was at Dr. Keston's suggestion, because of a low basal metabolic rate (−24 per cent), that she was given, in September 1944, ten doses of thyrotropic hormone. This apparently increased the uptake, *i.e.*, enhanced the functional activity, of the conspicuous metastasis in the 9th rib. Accordingly, on the purely theoretical grounds discussed above, a total thyroidectomy was performed on Oct. 17, 1944. Geiger counter examination in the operating room at the time of thyroidectomy was done to insure practically total removal of the gland (Fig. 2). (Parenthetically, it is of interest that no carcinoma was found in what remained of the thyroid gland three years after the removal of the local malignant adenoma.) Virtually all of the patient's functional thyroid tissue following elective total thyroidectomy, therefore, was neoplastic tissue. After recovery from this procedure, on Nov. 2, 1944, a therapeutic dose of radioactive iodine was administered, containing 20 micrograms of iodide ion, 9.4 millicuries of

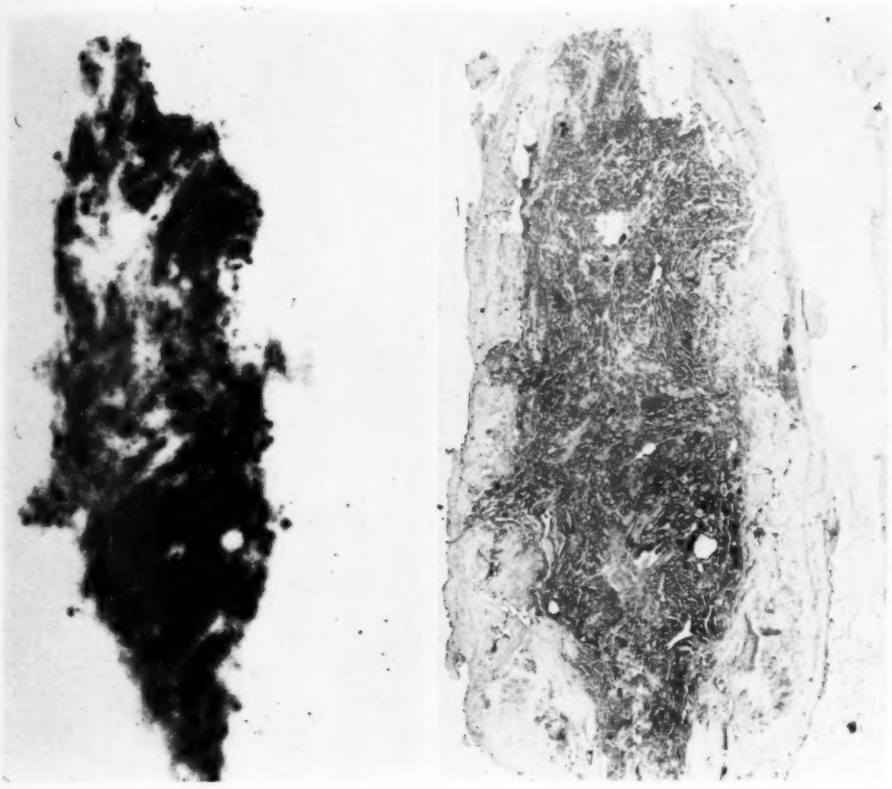

Fig. 3. Case 2, Table XI. Radioautograph of rib metastasis, adenoma malignum, Nov. 4, 1944. Histologic preparation separate from autograph. Note uniform heavy uptake of I^{131} outlining carcinoma with soft-tissue extensions into cortex of rib.

eight-day iodine, and 10.0 millicuries of twelve-hour radioiodine. Forty hours after this, the 9th rib containing a metastasis was resected (Fig. 3). Analysis by Dr. Keston of the metastasis in the rib showed that, by very conservative estimate, allowing for the bony tissue, there was uptake by the metastasis of 2 per cent of the original dose. Fractionation of the radioiodine present revealed a 14 per cent uptake in the thyroxine fraction, confirmed as such by repeated recrystallization of the potassium salt, ordinary thyroxine having been added to the fraction.

Five therapeutic doses of radioactive iodine, in all, were given between Nov. 2, 1944, and March 24, 1945, an approximate total of 45.0 millicuries of eight-day iodine and 85 millicuries of twelve-hour material. There was no significant lowering of the basal metabolic rate, even with total thyroidectomy added. Careful review of the films showed equivocal regression in only one lesion. A sixth much larger dose was given, therefore, on May 18, 1945, of 74 millicuries of eight-day and 96 of twelve-hour, making a total of 119 millicuries of eight-day iodine and 181 millicuries of twelve-hour material. (We were, by the way, indebted to Mr. L. D. Marinelli for many of the dosage measurements.) This last dose was given when the patient had a low white count, 2,750 with 62 per cent polymorphonuclear leukocytes. There was some further drop in the total white count but the polymorphonuclear leukocytes rose and the patient's complaints of depletion as a result of the dose may have been

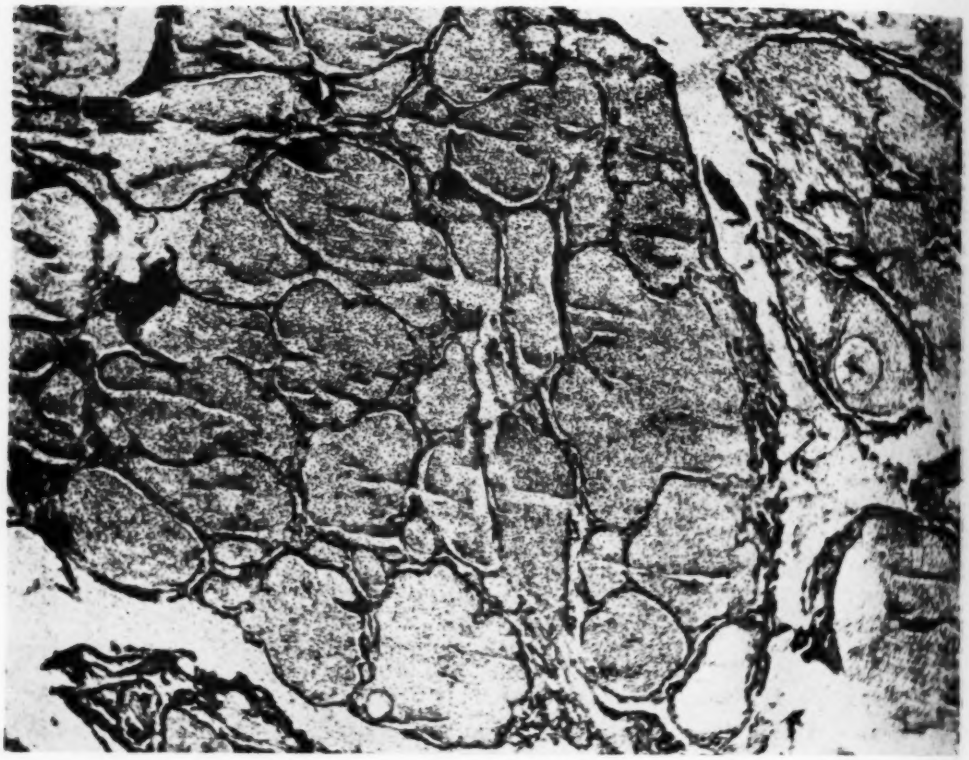

Fig. 4. Radioautograph of normal thyroid in a child of six years (Evans technic: tissue section mounted directly on photographic emulsion). Note the uniform distribution of radioactive material.

founded on fear, as she was aware of the possible significance of her leukopenia.

This case was also a failure of radioactive iodine therapy, possibly because of inadequate dosage. There was advance in all but one lesion in spite of therapy, and new foci developed. The patient finally succumbed, in another hospital, to generalized metastases. All was in readiness for a final tracer dose antemortem, but this was not administered because the end was unexpectedly rapid. Further disappointment was a limited autopsy permission. We were allowed to remove a specimen only from one lung. This, as expected, showed a well differentiated adenomatous lesion.

These three cases have laid the foundation for our present studies and plans for therapy. Tracer doses are now given in all cases of thyroid enlargement where there is any suspicion of malignant disease before operation. Uptake in the thyroid region is measured directly, as described by Werner, Quimby, and Schmidt (9). The urinary excretion pattern is also studied, and not infrequently the clinical diagnosis is altered by these findings, notably in the thyroiditis cases which simulate carcinoma. At the time of operation the surgeon and surgical pathologist examine the gross characteristics of the tissue *in situ*, almost always with confirmatory microscopic examination of quick frozen section. It is then decided whether partial or total thyroidectomy is indicated. Whenever possible, if malignancy is suspected, even in a single encapsulated nodule, adequate excision, often hemithyroidectomy, is done before the tissue is cut for frozen section diagnosis. There have been cases in our series where there was strong presumptive evidence that spillage of tumor at opera-

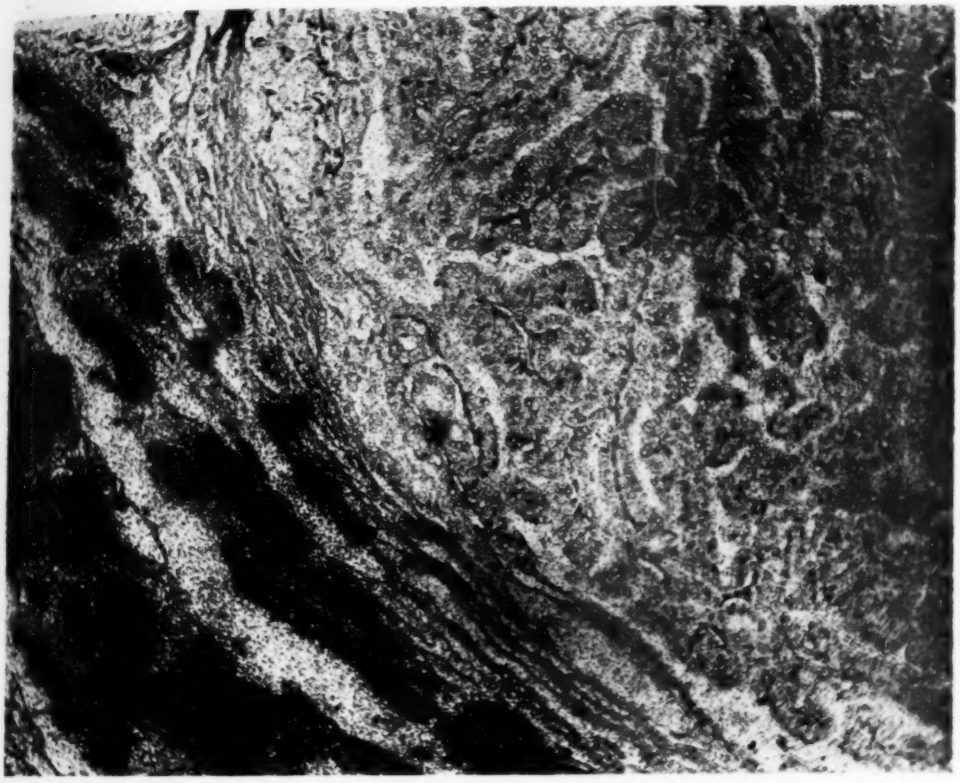

Fig. 5. Case 5, Table XII. Radioautograph of papillary carcinoma with rim of normal thyroid gland. Negligible uptake in pure papillary tumor.

tion had resulted in local implants, which later grew. This has occurred in two histological types, papillary and Hürthle-cell carcinomas.

After surgical excision, portions of the specimen are selected for direct measurement by Geiger counter and, if the uptake seems to warrant it, radioautographs are prepared by the method reported by Evans (10). The radioautographs have confirmed, in a general way, our interpretation of the relationship between the histological appearance and the functional activity of the neoplasm (Fig. 4). As material accumulates, it is clear that there are wider variations than we originally expected in the histology of tumors showing uptake.

To date, May 1, 1948, we have studied 68 cases of possible carcinoma of the thyroid with tracer doses of I^{131} (Table IX).

TABLE IX: I^{131} STUDIES*

Possible carcinoma	68
Proved thyroid carcinoma	32
Types of study:	
Tracer anteoperative	61
Tracer for metastases	15
Tracer for efficacy of total thyroidectomy	14

* To May 1, 1948.

The great majority of the patients were given preoperative doses for study of the primary tumor, but a few tracers were given before biopsy of a metastasis. Fifteen tracer studies, for metastases, have also been made by Geiger counter examination of the patient. Several cases for study were referred from other hospitals where the clinical work-up and the surgical treatment were carried out. Fourteen tracers have been given to determine the efficacy of total thyroidectomy; 11 of these were from our own surgical service, in 4 in-

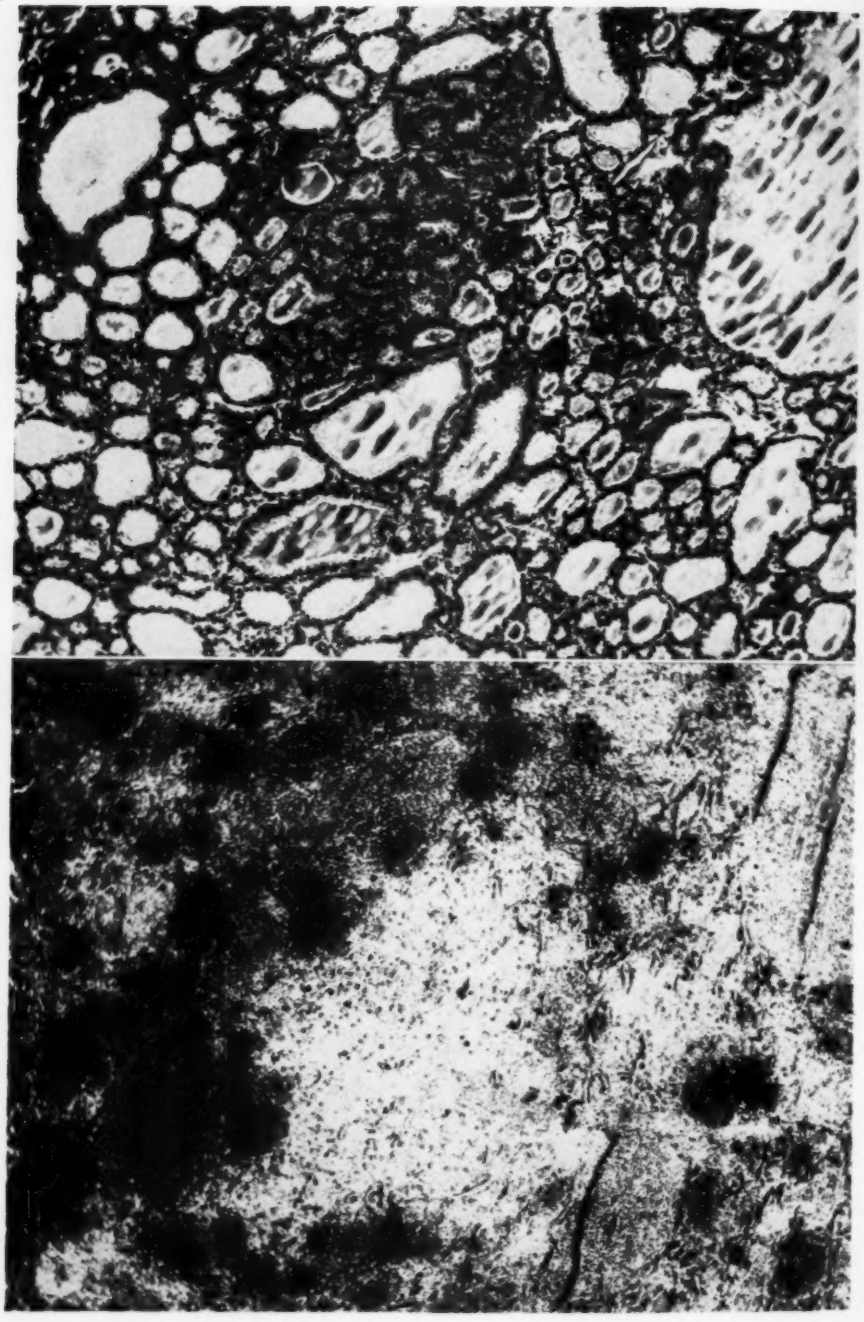

Fig. 6 (above). Photomicrograph of field in non-toxic nodular goiter, showing central locus of Hürthle cells.

Fig. 7 (below). Radioautograph of nearby section of the block showing absence of uptake in Hürthle cells. (Negative autographs of Hürthle-cell adenomas and carcinomas not suitable illustrations because blank.)

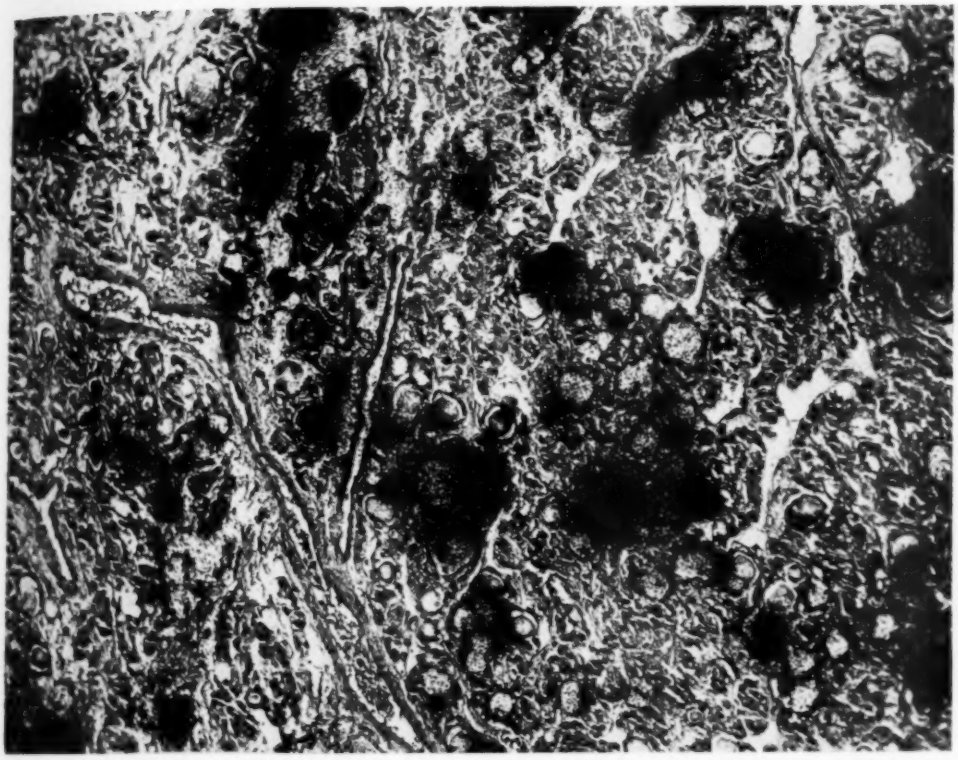

Fig. 8. Radioautograph of a field of non-toxic nodular goiter showing spotty uptake, with deposit chiefly in the smaller follicles. Adjacent small follicles, similar histologically, show no uptake.

stances with the Geiger counter brought to the operating room for examination of the surgical field before closure of the wound.

Thirty-two of the thyroid gland specimens from the 68 cases were not malignant tumors. Twenty-six of these benign lesions were nodular goiter cases, most of them fairly clear cut clinically, but with enough doubt to warrant examination with I^{131}—doubt cast by such disturbing findings as a history of long-standing goiter with recent rapid growth; an area of suspicious induration in a nodular gland; a single unduly firm nodule; a single nodule suddenly enlarging.

Of the remaining 6 benign lesions, 4 were inflammatory. Of these, 3 were chronic non-specific thyroiditis, 2 Hashimoto type, and 1 a Riedel type. The fourth inflammatory lesion was a chronic abscess with intermittent sinus formation following partial thyroidectomy—silk technic—done elsewhere.

The 2 last benign lesions were adenomas, one a Hürthle-cell type, which showed no uptake. In addition to these lesions of the gland itself there were 5 cases studied with tracer dose in which possible lymph node metastases were subject to biopsy. These biopsies were negative for thyroid carcinoma in all 5 cases.

Only 32 cancers, therefore, emerge for correlation of histology and function and for possible therapy. Table X shows their breakdown. As was expected, the undifferentiated Grade II and Grade III tumors showed no uptake of radioiodine. No case of pure papillary carcinoma to date has shown uptake (Fig. 5), nor any Hürthle-cell tumor (Figs. 6 and 7), benign or malignant. The uptake has been variable in the malignant adenoma group, and a

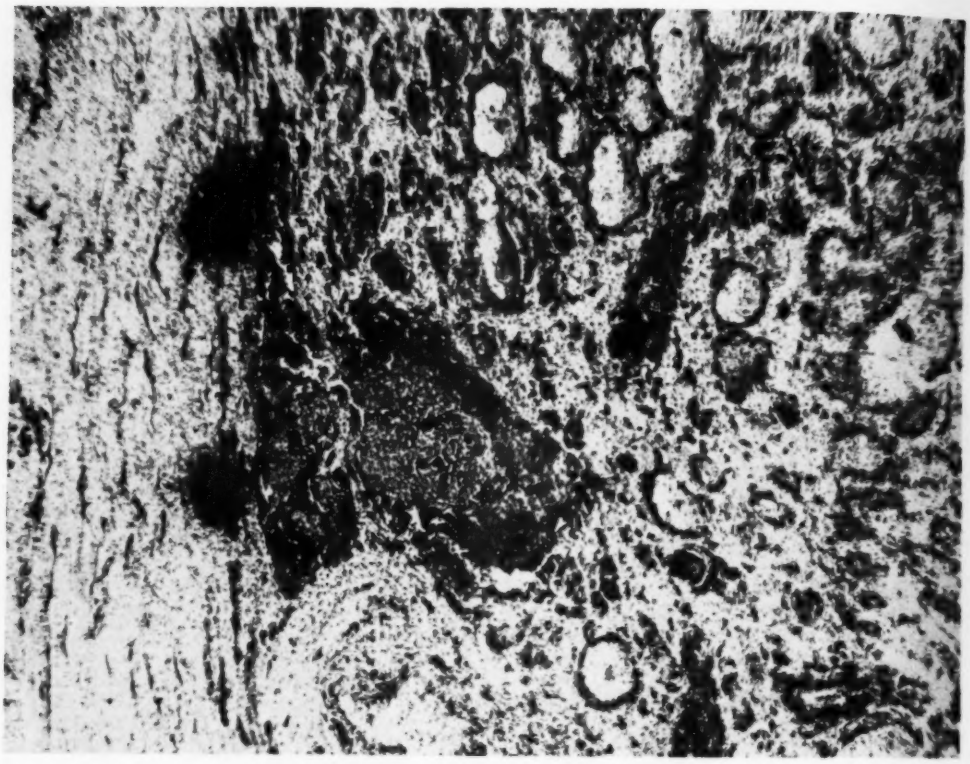

Fig. 9. Radioautograph from thyroid carcinoma metastasis. Concentration of radioiodine in small follicles at the periphery. (Courtesy of Dr. Evans: Radiology **49:** 212, 1947.)

TABLE X: TRACER STUDIES OF CARCINOMA OF THYROID WITH I^{131}*

Grade	Uptake	No Uptake	Total
I			
Adenoma malignum	7	5 (4 Hürthle cell)	12
Mixed	6 (4 aberrant)	0	6
Papillary	0	8	8
II	0	2	2
III	0	4	4
	13	19	32

* To May 1, 1948.

larger series is needed before we can affirm the hypothesis that the greater the degree of differentiation, the higher the functional activity. The presence or absence of the thyroid gland at the time of the tracer dose, the preparation of the patient, etc., are variables which must be taken into consideration before judging the function of a nodule from the thyroid itself. In biopsy of metastatic tumor with I^{131} study, the bulk of potential functioning tissue, the size of the dose, etc., are factors requiring evaluation. Studies on non-toxic nodular goiter (Fig. 8) show very spotty uptake in follicles which are similar in appearance histologically. Mean cell height in these lesions and in the neoplasms is so variable that measurements are probably invalid because of arbitrary selection of the fields. Small follicles at the periphery of some metastatic lesions, follicles which are lined by low cells and contain almost no colloid, have, by radioautograph, sometimes shown surprising density of darkening on the films (Fig. 9).

Eight malignant adenomas have been studied, in 7 of which there has been some uptake in the bone metastases. In the eighth there was no tracer before thyroidectomy at another hospital, and a solitary

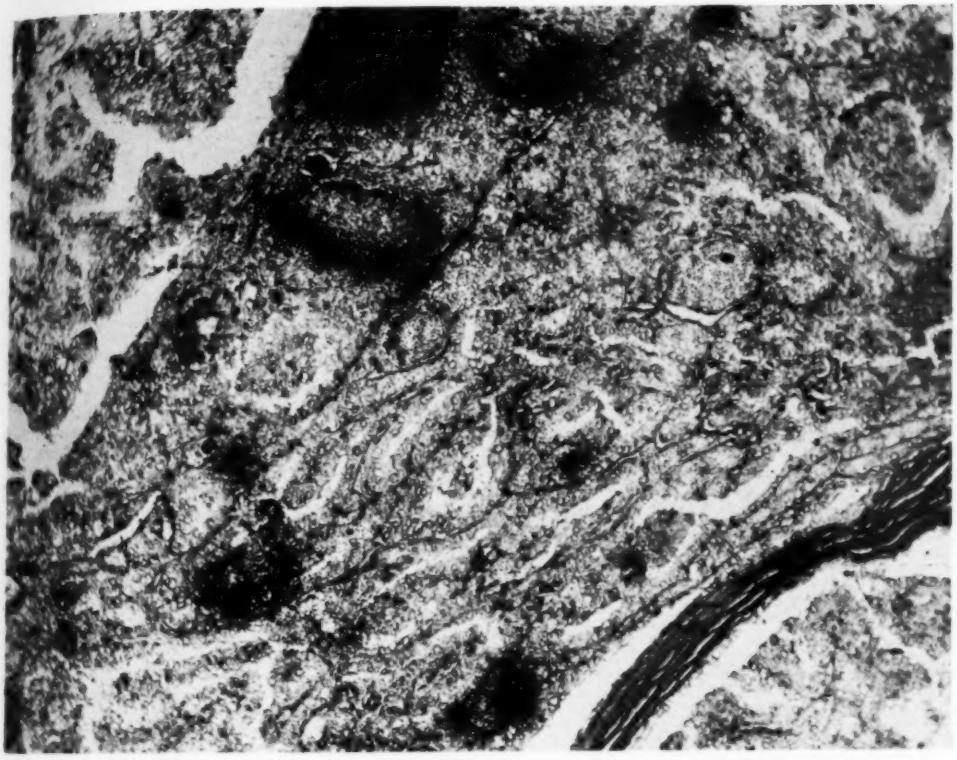

Fig. 10. Case 3, Table XII. Radioautograph of mixed papillary and adenomatous carcinoma showing spotty uptake in follicles among the papillae. This tissue was from a nodule in the lateral neck.

lung metastasis will be further studied after completion of thyroid ablation by I^{131} administration now in progress. Six mixed papillary and adenomatous tumors (Figs. 10, 12) have also shown some uptake, but this is probably a less favorable group for possible therapy with I^{131}. In these 14 cases which constitute our possible therapy group to date, there has been demonstrable uptake in the metastases in 7 cases.

Table XI shows those cases classified as malignant adenomas. Cases 1, 2, and 3 were failures of therapy and the patients are all dead, I^{131} never having been administered in Case 3 except in tracer doses. Case 4 has very widespread bone lesions and will be suitable for therapy only after ablation of the normal thyroid. This patient has already had considerable x-ray therapy and her lesions have been radiosensitive. Further external irradiation would not be possible because of skin damage. Case 5 is the one already mentioned, under study for a lung metastasis when inactivation of the thyroid itself shall have been completed by I^{131} and thyrotropic hormone perhaps administered.

In Cases 6, 7, and 8 total thyroidectomy has been done, and in Cases 6 and 7 a therapeutic dose of 50 millicuries has been given. These patients have only one demonstrable bone focus each. In Case 6 the metastasis in the spine has already been subjected to laminectomy for what was thought to be a myeloma, and a considerable portion of the neoplasm has therefore been removed surgically. The size of the lesion is impossible to determine and has been somewhat arbitrarily estimated to be 50 gm. In Case 7 the focus in the skull was measured at approximately 53 gm. by plaster cast and x-ray of skull defect.

TABLE XI: MALIGNANT ADENOMA WITH METASTASES

Case	Sex and Age	Thyroid Operation	Uptake Primary	Uptake Metastases	I^{131} Therapy	Present Status
Case 1 M. R.	F 40	Enucleation of encapsulated tumor	Not examined	In a few bone foci	Inadequate dosage	Died 16 years after onset, 11 years after operation, 5 years after metastases noted. Wide variation in histology at autopsy
Case 2 B. L.	F 48	1. Partial thyroidectomy 2. Total thyroidectomy	1. Not examined 2. No tumor	In all demonstrable bone foci	Inadequate dosage	Died 5 years after pathologic fracture and subsequent partial thyroidectomy. Widespread bone and tumor metastases, possibly brain
Case 3 J. M.	M 42	1. Enucleation 2. Total thyroidectomy	1. Not examined 2. No tumor	In all bone foci	No I^{131} therapy. Craniotomy for skull metastases	Died 9 years after operation. Metastases in bone and liver
Case 4 G. D.	F 55	Partial thyroidectomy. Excision of aberrant nodule	Not examined	In all bone foci	Awaiting thyroidectomy. (Tumor sensitive to previous x-ray therapy)	Living with osseous metastases 5 years after biopsy of metastasis
Case 5 J. R.	F 51	Partial thyroidectomy	Not examined	? in lung metastasis	50 mc. for thyroid ablation	Recent case; one week after dose
Case 6 M. T.	F 53	Total thyroidectomy	Uptake	High in single metastasis (spine)	50 mc. postoperatively for metastasis	Promising early response
Case 7 L. K.	M 52	Total thyroidectomy	Uptake	Slight in single metastasis (skull)	50 mc. postoperatively for metastasis	Considerable regression 3 weeks after dose
Case 8 A. K.*	F 56	Total thyroidectomy	None in tumor	High in sternal nodule. ? in vertebrae	Awaiting I^{131} therapy postoperatively	Recent case; 6 weeks after operation

* Courtesy of Dr. Ernest Gold, Gotham Hospital, New York.

These two cases showed little uptake in these foci until after removal of the thyroid gland. Studied then with tracer doses, the uptake was considerably increased in the bone lesions, measured as 12.5 per cent of the dose in the spine case and 2.5 per cent in the skull case. The high uptake in the spine case was especially encouraging, and increase in symptoms was striking beginning on the ninth day after the dose, which we estimated to be in the neighborhood of 15,000 e.r. This was strong presumptive evidence of radiation effect, further borne out by slow but steady regression of symptoms after the peak was reached, so that the present status is an improvement over the pre-dose condition. In Case 7, in spite of the low uptake, there has been a significant decrease in size of the skull lesion three weeks after the dose. Both these cases will presumably need further therapeutic doses and may well be candidates for thyrotropic hormone before administration of subsequent therapy.

In Case 8 there are two demonstrable bone lesions, one in the spine involving T-2, T-3, and T-4, and a large mass in the sternum. At the time of thyroidectomy this was shown to have no gross connection with the substernal extension of the tumor in the right lobe of the thyroid. There was a thin shell of bone palpable on the

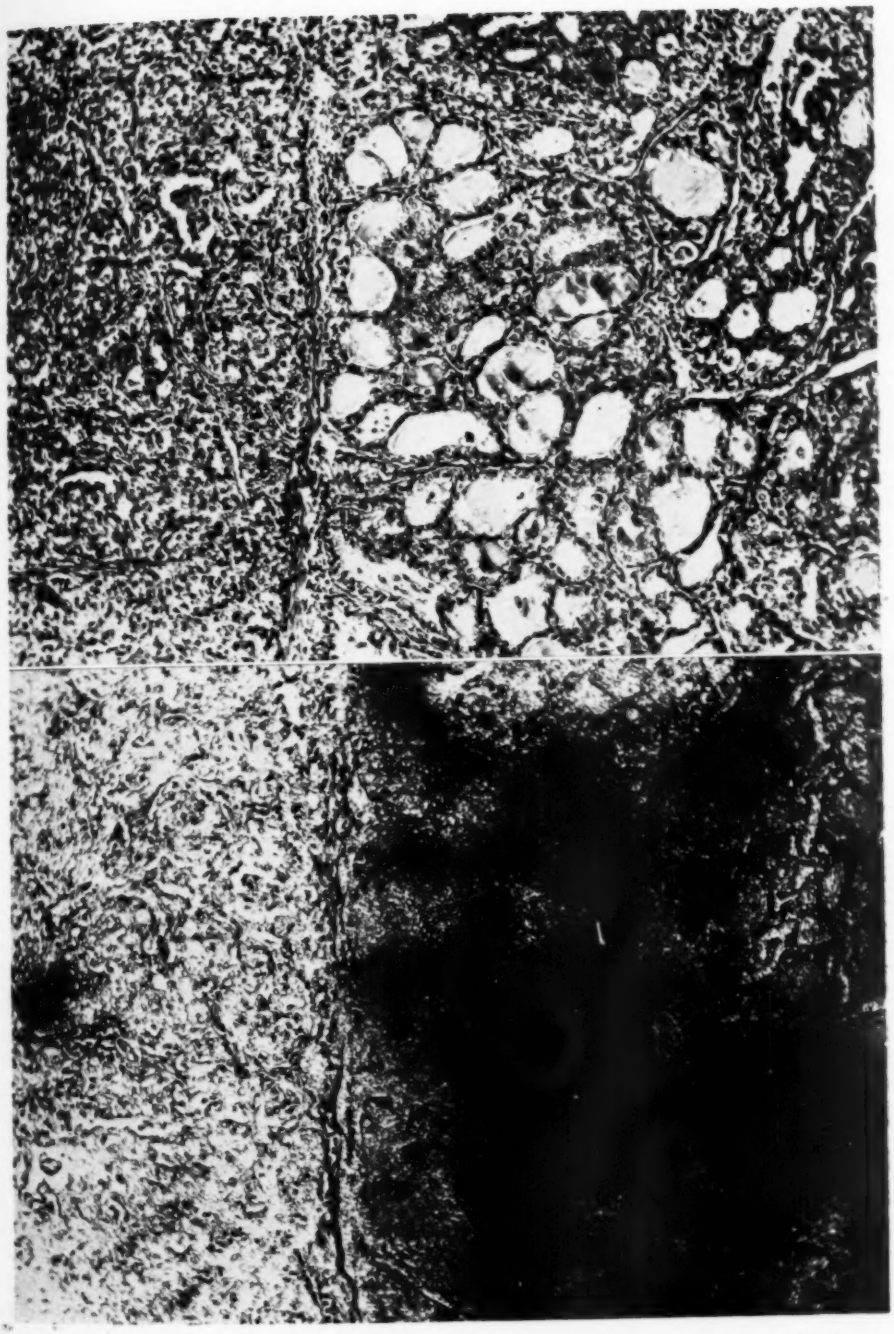

Fig. 11 (above). Case 4, Table XII. Photomicrograph of nodule from the lateral neck, showing in a single field marked variations in histology.

Fig. 12 (below). Radioautograph of a neighboring section from the block of Fig. 11, showing uptake in better differentiated portion of tumor.

TABLE XII: MIXED PAPILLARY AND ADENOMATOUS CARCINOMAS

Case	Sex and Age	Thyroid Operation	Uptake Primary	Uptake Metastasis	I^{131} Therapy	Present Status
A. G.	F 4	Total thyroidectomy and bilateral radical neck dissection	Not examined	Foci in neck	10 mc. to metastasis	Living with no clinical evidence of disease, 11 years postoperatively
D. S.	F 49	Partial thyroidectomy	Uptake	No uptake (lung)	None. Insufficient isotope	Died 26 months postoperatively. Metastases to lungs and bones
T. P.*	M 36?	Partial thyroidectomy	Not examined	Cervical lymph node	None. Insufficient isotope	Outside case. Lost to follow-up
E. N.†	F 22	Total thyroidectomy and bilateral radical neck dissection	Uptake	None demonstrated	5 mc. postoperatively, prophylactic	No recurrence, 15 months
R. W.	F 25	Total thyroidectomy and lateral neck dissection left	Uptake	None demonstrated	5 mc. postoperatively, prophylactic	No recurrence, 11 months
H. S.	M 26	Partial thyroidectomy and bilateral excision of neck nodules	Not examined	Lateral nodules	None	Four operations, 1944–48 for lateral nodules. Total thyroidectomy planned

* Courtesy of Dr. Bernard Roswit, Kingsbridge Veterans Hospital, New York.
† Courtesy of Dr. William MacFee, St. Luke's Hospital, New York.

posterior aspect of the sternum deep to the tumor. Three weeks after operation, in spite of the fact that the original tumor showed no uptake and uptake was minimal in the sternal nodule, 21 per cent of a tracer dose has been taken up by the sternal nodule. Measurement of uptake in the spine is less reliable. This case awaits a therapeutic dose and seems promising.

Table XII shows the cases classified as mixed types. It will be seen that 4 of these involve the lateral neck and 3 of the 4 have had total thyroidectomy as well as neck dissection. The first case is that of the child of four, with long survival, already outlined, but whether this good result is attributable to surgery alone or to adjuvant x-ray or I^{131} therapy it is not possible to say. Cases 2 and 3 were studied early, when we had material only for tracers, not for therapy, particularly since thyroidectomy had not been done. In Cases 4 and 5 total thyroidectomy was done, and these patients, who had not been shown to have any demonstrable distant foci, were allowed to develop myxedema and were then given prophylactic doses of 5 millicuries of I^{131} for possible tiny foci not removed surgically. The follow-up is short, and in view of what has already been said about the longevity in this particular group of young patients with lateral neck involvement, it may never be possible to know whether this prophylaxis was really indicated. We feel, however, that it is not potentially harmful as is postoperative external irradiation, and leaves the local field free for further surgery or for further irradiation of any kind should there be recurrence. We expect to pursue this policy in future cases of this kind. Case 6, in which a small remnant of thyroid gland is still left, is a candidate for this plan of therapy.

SUMMARY

We have presented a statistical analysis of our cases of thyroid carcinoma up to June 1, 1947, classified according to histologic types, together with possible five-year follow-up, a substantial number of

patients having been followed for much longer periods, up to seventeen years. We have not been able to evaluate the effect of local postoperative radiotherapy in these cases.

We have presented, as a preliminary report, to May 1, 1948, our studies with I^{131} of non-toxic thyroid lesions, benign and malignant, together with illustrative radioautographs, and outlined our present plan of therapy for two groups of cases: (1) the malignant functional adenomas with distant metastases, chiefly to bone; and (2) the tumors with multiple foci in the lateral neck, with or without involvement of the gland itself. We propose in both of these groups to perform an elective total thyroidectomy even if the primary focus has already been removed and there is no residual lesion (or perhaps no primary lesion!) in the gland itself. We think it reasonable to wait for the effect of thyroidectomy to make itself apparent in the hope that function of local or distant foci may be enhanced by physiological demand. In those with demonstrable metastases this may be further stimulated by administration of thyrotropic hormone. In the cases with bone metastases we intend to proceed further with doses of the order of 50 to 100 millicuries as indicated, and to the group with only local disease in the neck, radically removed at operation, we propose to give smaller postoperative prophylactic doses for possible small foci not removed surgically. Except in special circumstances we believe that surgical removal of the thyroid to facilitate I^{131} therapy is a better course than inactivating the gland by massive doses of the isotope, a time-consuming procedure during which the growth and physiology, and even perhaps the morphology, of the metastatic deposits may change the course of the disease and perhaps the effectiveness of internal irradiation by the isotope.

We are indebted to Charlotte Schmidt, B.A., for standardization of I^{131} material and for Geiger counts on patients and specimens, and to Grace Clarke, B.A., for preparation of radioautographs.

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(For Spanish Summary, see following page)

SUMARIO

Estudios con el Yodo Radioactivo del Carcinoma Tiroideo Funcional

Presentan los AA. un análisis estadístico de los casos de carcinoma tiroideo observados por ellos hasta el 1° de junio, 1947, clasificándolos conforme a tipo histológico, agregando en lo possible la observación subsiguiente de cinco años, aunque cierto número de enfermos fué observado por mucho más tiempo, hasta 17 años. En estos casos no resultó posible justipreciar el efecto de la radioterapia local postoperatoria.

En un estudio preliminar, que abarca hasta el 1° de mayo, 1948, preséntanse las observaciones realizadas con el I^{131} en lesiones tiroideas atóxicas, tanto benignas como malignas, junto con autorradiografías típicas, y bosquéjase el actual plan terapéutico seguido por los AA. en dos grupos de casos: (1) adenomas funcionales malignos con metástasis, principalmente óseas; y (2) tumores con múltiples focos en los lados del cuello, con o sin invasión de la glándula misma. Para ambos grupos propónese una pantiroidectomía electiva, aunque se haya extirpado el foco primario y no haya lesión residual (y quizás ni lesión primaria!) en la glándula misma. Parece lógico aguardar hasta que se haga sentir el efecto de la tiroidectomía con la esperanza de que las exigencias fisiológicas realcen la función de los focos locales o remotos. Cuando hay metástasis observables, la administración de hormona tirotropa puede excitar aun más dicha función. En los casos con metástasis óseas piénsase proseguir con dosis de 50 a 100 milicuries según esté indicado, y en el grupo que sólo muestra afección local en el cuello, extirpada radicalmente en la intervención, se administrarán menores dosis profilácticas postoperatoriamente con mira a atacar los posibles focos pequeños que no eliminara el bisturí. Salvo en circunstancias extraordinarias, la extirpación quirúrgica del tiroides a fin de facilitar el tratamiento con I^{131} es mejor que la inactivación de la glándula con dosis masivas del isotopo, procedimiento este prolijo durante el cual el crecimiento y la fisiología, y acaso hasta la morfología, de los depósitos metastáticos puede alterar la evolución de la enfermedad y tal vez la eficacia de la irradiación interna con el isotopo.

Factors Involved in the Experimental Therapy of Metastatic Thyroid Cancer with I^{131}

A Preliminary Report[1]

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THE TREATMENT OF metastatic thyroid cancer by radioactive iodine presents features of interest and importance to investigators concerned with the control of cancer by systemic means.

In terms of number of patients benefited, this subject does not loom large in the general field of cancer since encouraging results have been obtained in only a very small percentage of cases of an already uncommon type of tumor. Nevertheless, the causes of its success and its limitations should be worthy of thorough study because arrest of the disease has been attained in the presence of odds insurmountable by other forms of treatment (8, 9) The character of these few but definite successes strongly supports the long held view that if means were found to localize radioelements in tumors, important progress would be made toward control of the disease.

Efforts to localize radioelements in neoplastic cells have not been wanting in the past, but concentrations of practical value have not thus far been attained in cancer tissue *per se*. The premises upon which treatment of thyroid cancer by I^{131} is based are no exception to the rule, inasmuch as this therapy is possible only when cells of thyroid cancer share with the parent gland the pronounced avidity for the isotope. Under these conditions it is axiomatic to anticipate destruction of normal thyroid tissue in the process of tumor inactivation and to expect myxedema when good control of the disease is obtained. With this exception, and as in any other type of radiotherapeutic cancer treatment, the ultimate aim of the procedure is to achieve inactivation of the tumor with minimum damage to normal structures.

Locally, radioactive iodine will suit this purpose on account of the limited range of the beta radiation emitted, but the therapist is faced from the outset with the necessity of reducing the radiation dose to body structures which may be spatially removed from the tumors, but are very much in the metabolic path of the iodine. The experience gained in the last decade in the treatment of hyperthyroidism with I^{131} or I^{130} cannot be utilized fully in the treatment of thyroid cancer. In the case of hyperthyroidism, remission of symptoms is sought by partial inactivation of the thyroid gland, whereas in the case of cancer, radical devitalization of extensive tumor masses is attempted under conditions of differential uptake which as a rule are not as favorable (2, 4, 6).

Among tumors, only metastasizing struma approaches in magnitude and uniformity the avidity of the thyroid gland in Graves' disease. Other tumors, either primary or metastatic, which exhibit moderate preference for the isotope are those showing orderly cellular structure in follicular arrangement containing colloid-like material. Thus far only one example of thyroid carcinoma of high-grade malignancy has been reported to retain I^{131}, and this was a solid alveolar adenocarcinoma. The papillary and Hürthle-cell varieties, in our experience, have shown no retention. Studies of thick-section radioautographs,

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[2] On leave of absence to the Argonne National Laboratory, Chicago 80, Ill.

which reveal the extent to which tumor can be irradiated by the corpuscular rays of the isotope, have proved disappointing because, as a rule, uniformity of irradiation is seldom obtained. The realization that many parts of a tumor are left practically untouched has discouraged therapeutic attempts with the isotope when treatment with more conventional means is not contraindicated. For this reason it was decided to confine this experimental type of therapy to the later stages of the disease. This decision was also favored by the fact that distant metastases, as a rule, are well suited to the objective *in vivo* study of tumor physiology with I^{131}.

This presentation is a sketchy progress report based on twelve months experience at Memorial Hospital. This investigation has required the co-operative efforts of four departments, namely: Surgery, Pathology, Clinical Investigation, and Physics. In a subject so devoid of experimental background, it has been found necessary to arrive at decisions as to treatment and study through weekly conferences involving members of the four departments and of Dr. Rulon W. Rawson, who has joined the group in a major consulting capacity for the last six months. A detailed presentation of results would be beyond the scope of any one paper. It is proposed to report in detail on the various subjects of physiology, physical methodology, therapy, and pathology as outlined below, as soon as results warrant it.

METHODOLOGY
- (1) Instrumentation
- (2) Measurements *in vivo*
- (3) Measurement of samples
- (4) Radiation dosimetry
- (5) Radioautography

THERAPY
- A. Clinical Material
  - (1) Selection of cases; tumor type
  - (2) Age, sex
  - (3) Duration of disease
  - (4) Previous treatment
- B. Results. Effects on:
  - (1) Primary tumor
  - (2) Metastasis
  - (3) Normal thyroid
  - (4) General metabolism
  - (5) Blood and marrow
  - (6) Kidney
  - (7) Liver
  - (8) Electrolyte balance
  - (9) Other observations

PHYSIOLOGY
- A. Attempts to Modify Collection of Iodine by Cancers of the Thyroid by:
  - (1) Thyroidectomy
  - (2) Thiouracil and derivatives
  - (3) Thyrotropic hormone
  - (4) Thyroid extract or thyroxin
  - (5) Alteration of renal excretion of iodine
    - (*a*) Hypotensives
    - (*b*) Altered chloride intake
    - (*c*) Pitressin
    - (*d*) Hormones
- B. Metabolism of Iodine
  - (1) Cross distribution (postmortem studies)
  - (2) Plasma proteins
  - (3) Urine iodine content

In the course of the past year, 18 thyroid cancer patients have been investigated to determine their suitability for treatment with I^{131}. In all of them metastases were present. Nine of them were chosen for treatment and exhaustive studies, but in only 2 of these did satisfactory initial retention of I^{131} in the tumor warrant immediate experimental therapy with massive doses. Presentation of one of these cases follows:

In F. K., a male 53 years old, the disease was first diagnosed in February 1939, following pain from metastasis to the right hip. Biopsy at the time revealed alveolar adenocarcinoma of the thyroid. The primary tumor was discovered in the left lobe of the thyroid and excised in June 1941. The patient was first seen at Memorial the following month. Numerous metastases appeared in seven ribs, seven vertebrae, the left femur, right shoulder, and in the anterior portion of the right iliac bone. In the interval from 1941 until 1946, the course was steadily downhill although unusually good palliation was obtained from occasional x-ray therapy. In the summer of 1944 it was found that the lesions concentrated I^{131}, but no therapy could be attempted because the isotope was not available in large quantities. Not until September 29, 1946, could the patient be admitted for therapy. At the time he weighed only 86 pounds and was nearly moribund, being literally skin and bones; unable to move in bed; taking a grain and a half of morphine every two hours, and still suffering excruciating pain. His daily food intake for the previous four to six weeks had been measured in tablespoonfuls of soup, broth, or milk.

A rapid x-ray survey of all the bones served as

the basis for an estimated total mass of tumor tissue of roughly 2 kg. Since it was obvious that, unless treatment were to be promptly effective, the patient might soon be dead, on Oct. 2, two days after a small tracer dose, 60 millicuries of radioiodine, I^{131}, were given orally, and seven days later, on Oct. 9, a larger dose of 121 millicuries was given orally. A number of definite improvements followed, and at about forty days (Nov. 1) the patient could leave the bed to have his picture taken. Soon afterward, however, severe, almost fatal complications occurred, which were managed expertly by the Department of Clinical Investigation. These complications fell within the picture of an acute thyrotoxicosis of unusual severity. The hypothesis was advanced that under the influence of intracellular radiation, the thyroid follicle cells of the tumors had broken down, thereby releasing large amounts of thyroglobulin in the organism. To verify this hypothesis, a blood specimen was drawn and sent to Dr. William Salter at New Haven for a total iodine and a protein-bound iodine analysis. Dr. Salter's report of 26 micrograms of protein-bound iodine per 100 c.c. of plasma served adequately to confirm the suggested mechanism. On the sixtieth day, while the thyrotoxic symptoms were gradually clearing, a squamous-cell carcinoma of the larynx appeared suddenly and was treated by x-rays within the next thirty days.

By the ninetieth day the patient seemed well enough to resume treatment, but the thyrotoxic symptoms reappeared as soon as effective doses of I^{131} were tried. On June 11, seventy-two hours after stopping a seventy-six-day course of propylthiouracil, which had been administered in an attempt to empty the tumors of their stored thyroglobulin, a dose of 122 millicuries of radioactive iodine was given and was this time followed by no reaction of any kind. The serum protein-bound iodine level had fallen during the seventy-six days of propylthiouracil to less than 1 microgram per 100 c.c. of blood. The patient has now been discharged to his home, having gained about 55 pounds of weight, and being free of pain except for occasional twinges in the left leg. He is able to drive his own car, and to do odd jobs about his house, although he still must use crutches because the large tumor in the right ilium had almost obliterated all normal structures. There is unquestionably still considerable viable neoplastic tissue in this man's body, but his improvement has been of a high order of magnitude.

DISCUSSION

Though it would be presumptuous at this time to attempt specification of dosage and technics with the accuracy prevailing in conventional radiation therapy, it should be fruitful to consider on very broad lines the radiotherapeutic factors involved.

In its simplest terms, the aim of the method is to deliver to the tumors a therapeutically effective dose T_t in equivalent roentgens (e.r.) without producing irreversible damage to normal body structure. On the basis of radiological experience, the hemopoietic system, on account of its importance and its radiosensitivity, could represent the structure to be spared; for the purpose of this discussion, it may be assumed that it should not receive a dose higher than T_h equivalent roentgens; in order to establish some order of magnitude, we may assume that $T_t = 6000 - 30{,}000$ *e.r.* and $T_h = 100 - 500$ *e.r.*[2]

If these doses are representative of the variations encountered in human material effective therapy could be achieved with I^{131} concentrations as low as those corresponding to a dose ratio $T_t/T_h = 12$ in those patients combining maximum tumor radiosensitivity with maximum hemopoietic radioresistance, whereas, at the other extreme, dose ratios T_t/T_h as high as 300 would be necessary.

It is readily recognized that this range is much too wide to be of practical use in deciding routinely upon therapy of individual cases; yet it does provide a guide upon which experimental therapy with I^{131} or other internally administered radioelements could be based.

For any given patient this uncertainty could be reduced somewhat by: (*a*) ascertaining the response of a single lesion to external x-ray therapy or interstitial radiation; (*b*) determining the tumor dose by intelligent estimates of tumor volume; the I^{131} content and its effective half-life by repeated external measurements with suitably calibrated Geiger-Müller counters; (*c*) calculating the "marrow" dose by assuming it approximately equal to the dose received by the blood. The latter can be easily calculated on the basis of I^{131} concentration as a function of time following the administration of tracer doses (5).

[2] These figures do not aim at any great accuracy. The limits for T_h were based on roentgentherapy experience correlated to integral doses expressed in megagram-roentgens (1) and on therapeutic use of P^{32} (3); the lower limit for T_t is based on tumor doses available with x-ray therapy, the highest on the basis of interstitial radiation.

No known procedures, however, are at hand which can provide information on two other important factors: namely, whole body radiosensitivity and distribution of I^{131} within all tumors.[3]

Therefore, in the face of these unknowns, it is important to search for physiological means which, on the one hand, enhance both the concentration and permanence of the isotope in tumor tissue and, on the other, favor its rapid elimination from the most vulnerable parts of the body.

In the last year or so, at our institution several procedures have been investigated in connection with I^{131} therapy. They are: thyroidectomy, administration of thyrotropic hormone, administration of anti-thyroid medication, and alteration of renal function. The use of others is planned for the future. No claim can as yet be made as to their correct therapeutic use. It is not known, for instance, whether they cause singly or in combination any change in radiosensitivity in tumor or normal tissue which ultimately would enhance or reduce the advantage obtained by their ability to increase the retentive capacity of functional thyroid tumors. Although high concentration in tumor is obviously desirable, this factor may very well rank second to homogeneity of distribution within the tumor as a prerequisite to favorable prognosis.

On the basis of our limited knowledge about the influence of the above mentioned factors, and the impossibility of obtaining pertinent information on animal thyroid tumors on account of their rarity, it is premature to set more rational criteria on the strength of which therapy of this type should be instituted. Faced with terminal cases, the tendency often has been to raise the dose administered to the highest level consistent with reasonable safety.

Physical calculations based on concentration of body fluids (blood, sputum, gastric juice, and urine) suggest caution in administering doses of the order of 100 millicuries or more and alertness in detecting early radiation damage. Means ought to be found to decrease the isotope concentration in the sputum, gastric juice, and urine without impairing concentration in the tumors.

In the course of the past year, the Department of Clinical Investigation has performed thorough tests to appraise radiation damage to marrow, kidney, and liver. Nothing highly significant has been found to date with the exception of transient and moderate lowering of the blood count, transient impairment of salivation accompanied sometimes by dryness of the mouth, and occasional symptoms of cystitis. Doses administered have been as high as 186 millicuries of I^{131} within a period of one week (patient F. K.) and as much as 550 millicuries within a period of ten months in another. Recently we have given single doses of about 200 millicuries to several patients, but insufficient time has elapsed to appraise radiation damage. The outstanding example of immediate danger has been the thyrotoxicosis in the case reported above (F. K.). Of the physiological means designed to alter the collection of I^{131} in tumors, thyroidectomy—whether surgical or by means of the isotope—has produced some encouraging results. These have been presented elsewhere (7). In conclusion, it is felt that our experience justifies further clinical trial of I^{131} therapy in the treatment of selected cases of metastatic thyroid cancer.

[3] Neither are data available on the question whether one equivalent roentgen (r.e.p.) provided by I^{131} is biologically equivalent to one tissue roentgen of x- or gamma-ray radiation. Present experience—with due regard to the uncertainties involved—suggests that the calculated r.e.p.'s necessary for tumor regression are substantially higher than those reported by conventional radiation therapy. It is idle to speculate on the reasons for this without entering into an exhaustive study of the subject. It is proposed to do so in a forthcoming publication.

SUMMARY

A rational basis for the therapy of functional metastatic thyroid cancer depends on many physiological and radiological factors which are mostly unknown or difficult to determine with suitable accuracy.

Physical calculations and radiological experience provide, however, some broad quantitative data upon which experimental therapy could be based. Particular attention should be paid to the hemopoietic system and to body structures which are bathed by fluids of high I^{131} concentration.

Preliminary results warrant further clinical trial of this type of therapy.

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SUMARIO

Factores Participantes en el Tratamiento Experimental con I^{131} de las Metástasis del Cáncer Tiroideo. Informe Preliminar

Una base lógica para el tratamiento de las metástasis del cáncer tiroideo comprende muchos factores fisiológicos y radiológicos, en su mayoría desconocidos o difíciles de determinar con bastante exactitud. Los cálculos físicos y las observaciones radiológicas aportan, sin embargo, algunos amplios datos cuantitativos en que los que podría basarse la terapéutica experimental. Hay que conceder suma atención al aparato hematopoyético y a los tejidos orgánicos bañados por humores en que el I^{131} alcanza concentraciones altas. Los resultados preliminares justifican nuevas pruebas clínicas de esta terapéutica.

Descríbese uno de los dos casos en los cuales la satisfactoria retención inicial de I^{131} en el tumor pareció justificar el tratamiento experimental con dosis masivas. Un tumor primario del lóbulo izquierdo del tiroides había sido extirpado en 1941, pero había presentes metástasis óseas dispersas. En el verano de 1944 averiguóse que dichas lesiones concentraban I^{131}, pero hubo que aguardar hasta 1946 para conseguir el isotopo en cantidad suficiente para aplicar el tratamiento. Aunque el enfermo se hallaba casi moribundo, la administración de grandes dosis del isotopo fué seguida al principio de mejoría bien definida. Una grave tirotoxicosis que se presentó obligó, sin embargo, a abandonar el tratamiento. Ofrecióse la hipótesis de que, bajo el influjo de la radiación intracelular, se habían desintegrado las células de los folículos tiroideos, liberando así grandes cantidades de tiroglobulina en el organismo, y esto fué confirmado por el estudio apropiado de un ejemplar sanguíneo, que reveló 26 microgramos de yodo combinado con proteína por 100 cc. de plasma. Administróse entonces una serie de propiltiouracilo con la idea de vaciar la tiroglobulina fijada, de los tumores, y a continuación, se administró otra dosis de yodo radioactivo, sin producir la menor reacción contraproducente. La mejoría obtenida fué de gran magnitud, si bien todavía queda manifiestamente una considerable cantidad de tejido neoplásico viable en el cuerpo del paciente.

Treatment of Hyperthyroidism with Radioactive Iodine[1]

(I^{130}, 12-Hour Half-Life and I^{131}, 8-Day Half-Life)

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ROENTGEN DISCOVERED the rays that bear his name in 1895. Madame Curie separated radium from pitchblende in 1898. Henri Becquerel in 1901 carried a small vial of radium in his pocket, and the reaction produced on the skin of his belly led him to see Dr. Ernest Besnier. Therein was produced the idea of treating diseased tissues by means of radioactive materials. In 1905, Dr. Robert Abbé (1) reported the first case of hyperthyroidism successfully treated by implanting radium directly into the substance of the thyroid gland. Treatment by means of x-rays directed externally over the thyroid has also been used effectively.

The next great advance in the radiation treatment of the hyperplastic thyroid began in 1936 through the stimulation of medical men by Dr. Karl T. Compton of the Massachusetts Institute of Technology. Thereafter, followed a series of co-operative researches undertaken by the Massachusetts Institute of Technology and the Massachusetts General Hospital. Prof. Robley D. Evans, Dr. Saul Hertz (2), and their associates worked out the physiologic behavior of radioactive iodine in animals and later in humans. In 1941, Hertz first tried the treatment of hyperthyroidism with the combination of radioactive iodine and potassium iodide (3). In 1943, it fell to two of the present writers (Chapman and Evans, 4) to carry on this work and we then felt that we could not be certain whether those patients of Hertz who had improved were responding to the radioactive iodine, the ordinary iodine, or their combination. Consequently, we decided that the definitive use of radioactive iodine could be established best by a program that would cover five points:

TABLE I: DATA ON 130 PATIENTS WITH HYPERTHYROIDISM TREATED ONLY WITH RADIOACTIVE IODINE, 1943–48

65 Given I^{130} 12-Hour, 1943–46		65 Given I^{131}, 8-Day, Aug. 1946–Feb. 1948
45 gm.	←Average estimated thyroid weight →	50 gm.
32 millicuries (14–79)	Average single effective dose by mouth	10 millicuries (4–14)
0.45 millicurie/gm.	Average single effective dose retained per gram thyroid	0.14 millicurie/gm.
6	Radiation sickness	0
3 days	97 per cent of radiation delivered in approximately	30 days
15*	Given second doses	4
1 month	Average interval to normal basal metabolism rate	2 months
51	Responded and continue well	52
11	Resulting hypothyroidism	4
3	Better, but toxic 6 months after treatment	8
0	Died	1 (myocardial infarction 19 days after treatment)
0	Recurrence of disease	0
65		65

* Five of these received I^{131} for their second dose; the other 10 received I^{130}.

[1] From the Thyroid Clinic of the Massachusetts General Hospital and the Radioactivity Center of the Laboratory of Nuclear Science and Engineering of the Massachusetts Institute of Technology. Presented at the Thirty-third Annual Meeting of the Radiological Society of North America, Boston, Mass., Nov. 30–Dec. 5, 1947.

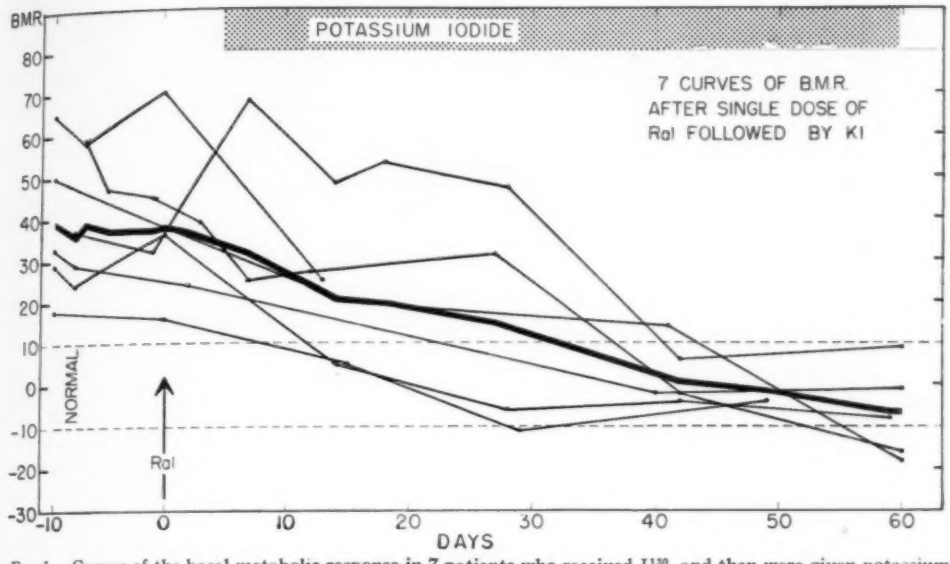

Fig. 1. Curves of the basal metabolic response in 7 patients who received I^{130}, and then were given potassium iodide by mouth. The average curve of response is identical with that seen in other cases where ordinary iodine was not given.

1. The use of radioactive iodine alone.
2. The definition of a single effective dose; the duration of its effect; the pattern of relapse, if any, of thyrotoxicosis.
3. The production of myxedema by a single dose.
4. The observation of the histologic changes in the same gland both before and after such treatment.
5. The observation of the toxic effects of radioactive iodine.

Between 1943 and 1947, we treated 65 hyperthyroid patients with radioactive iodine having a half-life of twelve hours, isotope I^{130}. Between August 1946 and the present, we have treated another 65 patients with the eight-day isotope, I^{131}. The results in these 130 patients are summarized in Table I.

Table II shows the doses employed in the last 27 patients treated with the twelve-hour isotope, I^{130}, and Fig. 1 indicates the response of the basal metabolic rate in 7 patients who received I^{130} followed by potassium iodide. Figures 2–6 illustrate observations in individual cases.

It appears that we have answered most of our original five points. Radioactive iodine I^{130} with a half-life of twelve hours has been used effectively—alone—in a single retained dose averaging 20 millicuries or 0.45 millicurie per estimated gram of thyroid, 90 per cent of whose radiation dose is delivered in the first thirty-six hours. Myxedema has been produced. The histologic changes seen in the thyroids one and two years after treatment show fibrosis and regenerative hyperplasia, according to the unanimous judgment of five of the nation's outstanding pathologists. Relapse or recurrence of hyperthyroidism has not been observed, although we are continuing to keep these patients under observation. Toxic effects of this short-lived form of radioactivity have been nausea, slight fever, and swelling and tenderness of the thyroid for a few days. No later evidences of ill effects have been observed. Effective doses in the second

TABLE II: DOSES OF I^{130} (TWELVE-HOUR RADIOACTIVE IODINE) RECEIVED BY 27 PATIENTS, MAY 1945–MAY 1946

Average dose by mouth	32.6 millicuries
Average dose retained	20.0 millicuries
Average dose retained: millicuries/gram thyroid	0.45 millicurie

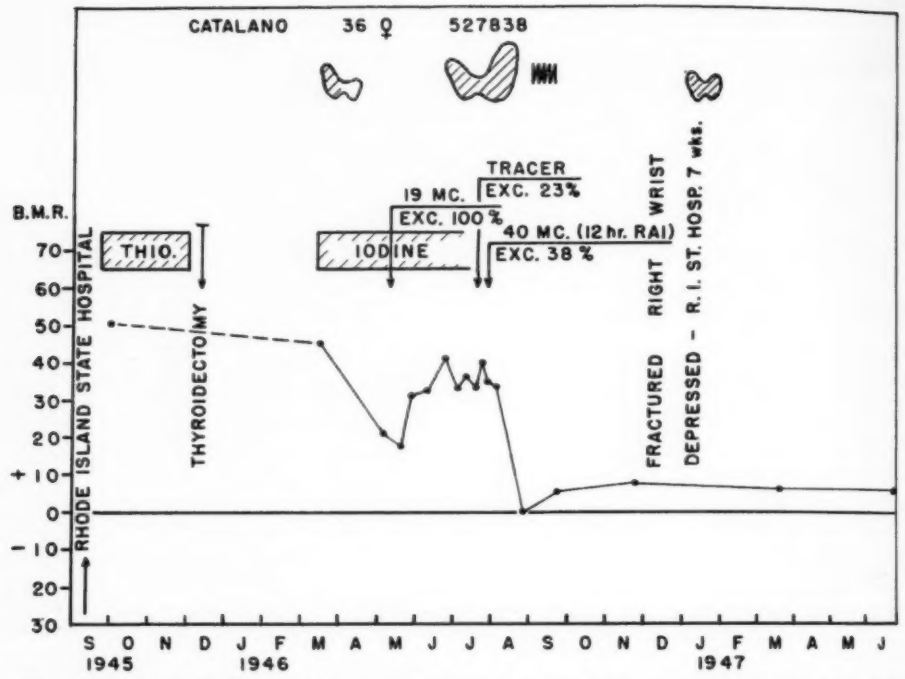

Fig. 2. Response of a 36-year-old woman who was found to be thyrotoxic while in a mental hospital. Subtotal thyroidectomy produced no lasting benefit, and the patient came to us while toxic and taking iodine. She was given 19 millicuries of I^{130} while taking iodine and, as expected, she excreted 100 per cent of the dose. Later the iodine was stopped and in three weeks a tracer dose indicated that the thyroid retained about 77 per cent of the dose. We therefore predicted that a therapeutic dose would be effective. There was a prompt response to 40 millicuries and basal metabolic rates have since been normal.

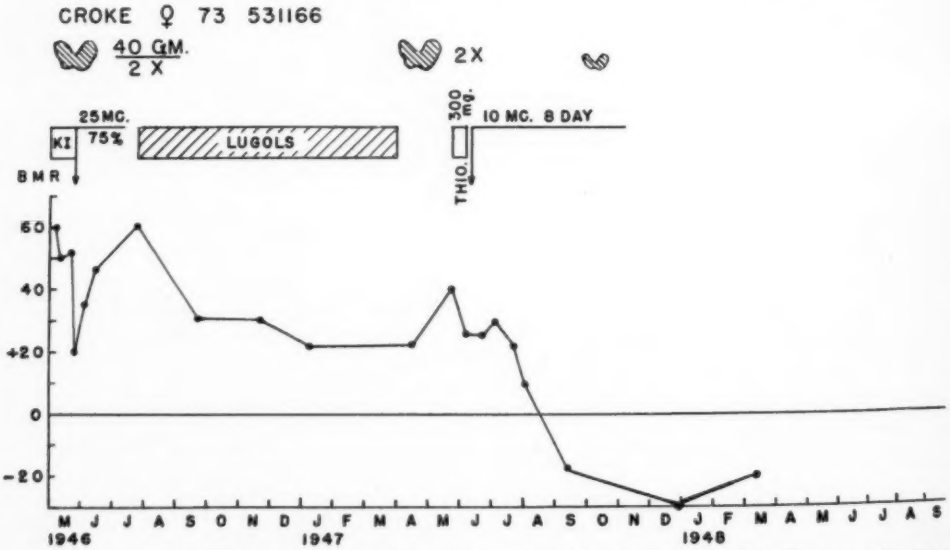

Fig. 3. Course of a 73-year-old thyrocardiac, a poor surgical risk, who was given 25 millicuries of I^{130} while taking iodine. Although she excreted 75 per cent of the dose, there was a temporary response to treatment. She was controlled on iodine until a severe heart attack made definitive treatment necessary. After taking thiouracil for two weeks, she omitted all treatment for three days and then swallowed 10 millicuries of the eight-day isotope. Thereafter she declined into a myxedematous state, which is considered beneficial for her cardiac symptoms.

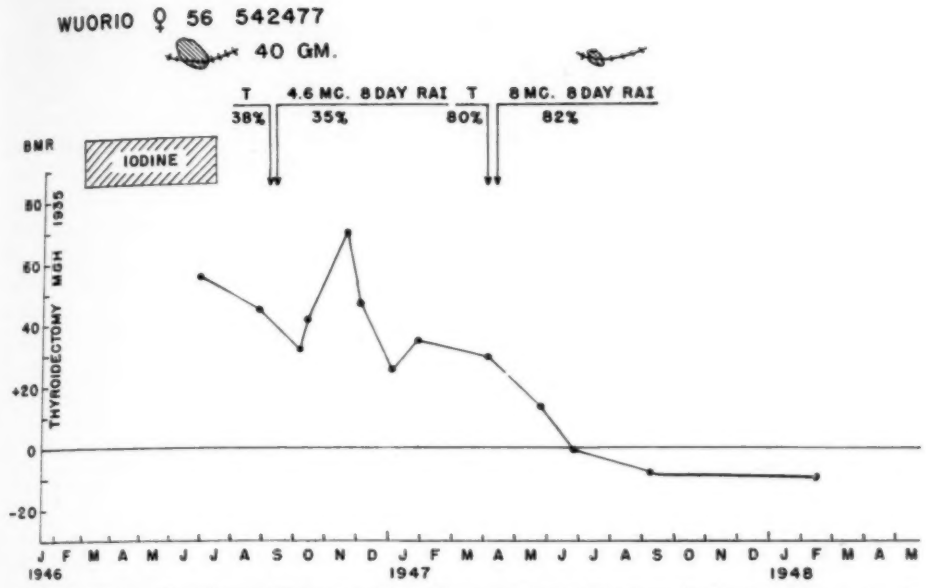

Fig. 4. Course of a 56-year-old woman whose disease returned after thyroidectomy. She was one of the first treated with the new isotope (I^{131}) from Oak Ridge and was given a cautious low dose. Thereafter, there was a temporary rise in the basal metabolic rate and exacerbation of symptoms. We have observed this in a few others, with an associated elevation of the protein-bound iodine. Following our established policy, we allowed six months to elapse before giving a second dose of 8 millicuries by mouth. To this the patient has responded further despite the rather high excretion.

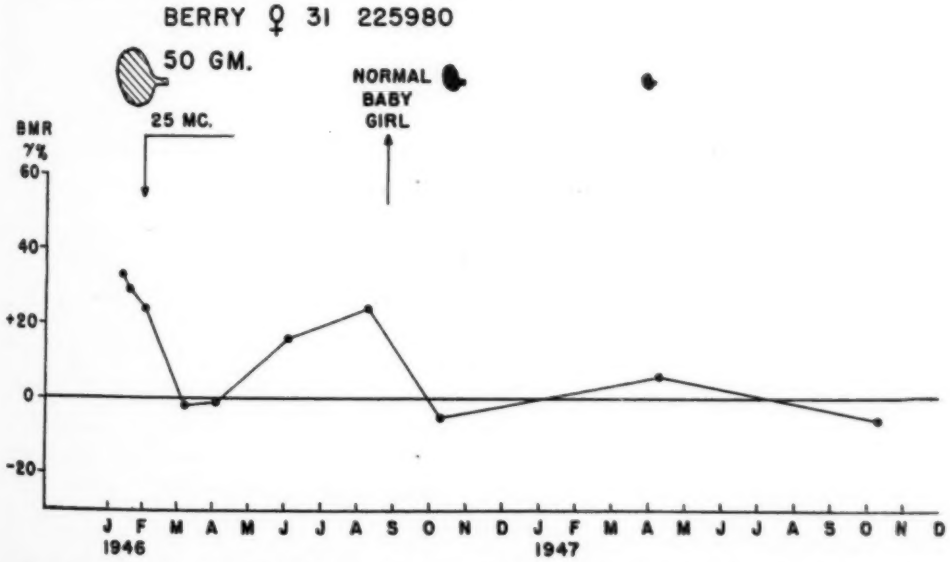

Fig. 5. A 31-year-old woman had undergone 2 previous thyroidectomies and had recurrent thyrotoxicosis with severe exophthalmos. She was prepared for treatment with the twelve-hour isotope, but a few days before the cyclotron was to produce the dose, she admitted pregnancy, about the second month. The experimental nature of the treatment was explained, a tracer dose of radioactive iodine was given, and no activity was evident by Geiger counter over the pelvis. The following day, 25 millicuries of I^{130} was given by mouth, and a good response was obtained. Late in pregnancy, the basal metabolic rate rose. This was interpreted by some as a sign of recurrent disease; by others it was regarded as the physiologic rise incident to pregnancy. Since delivery both mother and child have been normal.

and fifth months of pregnancy have not caused cretinism or recognized changes in the children, who appear healthy, but we advise against use of the isotope in pregnancy beyond the third month.

From our short experience with the eight-day isotope, I^{131}, we can summarize as follows:

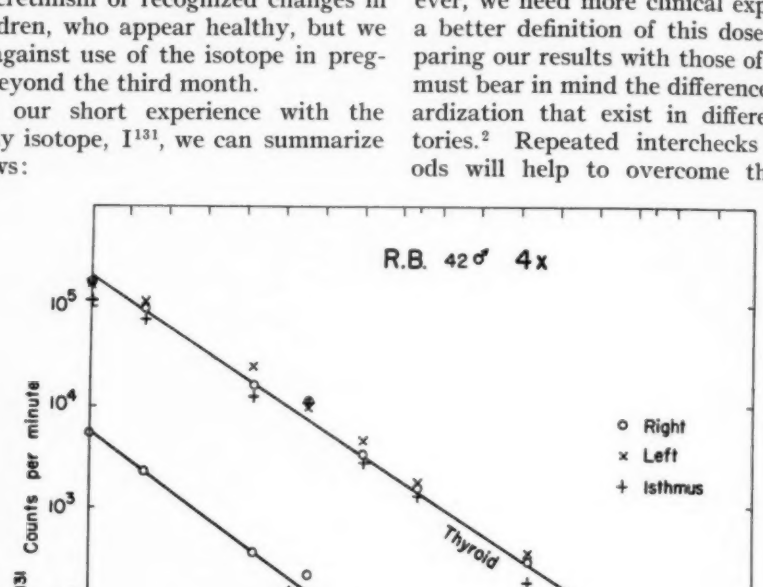

Fig. 6. Radioactivity of the I^{131} retained in a hyperfunctioning thyroid. The activity decreased exponentially with time, over the period of about seventy-five days studied, but fell to half value in six days, instead of in eight days as would be observed for I^{131} alone *in vitro*. This increased rate of disappearance *in vivo* is due to loss of I^{131} from the gland, which has a half-period of $1/(1/8 - 1/6) = 24$ days. The activity remaining after thirty days, or five *in vivo* half-periods, is then $(1/2)^5 = 1/32 = 3$ per cent. Consequently 97 per cent of the total radiation dose is delivered in the first thirty days after administration of the I^{131}.

1. Radioactive iodine with a half-life of eight days is an effective single therapeutic agent. In 41 of the patients who responded the average retained dose was 0.142 millicurie (142 microcuries) per estimated gram of thyroid tissue; 97 per cent of this dose of radiation is delivered in thirty days. In most cases, the administered effective dose was from 8 to 14 millicuries by mouth.

2. The single dose which by our standards has proved to be effective is 142 microcuries per gram of thyroid. However, we need more clinical experience for a better definition of this dose. In comparing our results with those of others, we must bear in mind the differences in standardization that exist in different laboratories.[2] Repeated interchecks on methods will help to overcome this present difficulty. No relapse of disease has been seen. Failure to respond, or response in part, is interpreted now as a matter of the lack of proper dose in relation to the functional activity of the particular human thyroid.

3. Myxedema has been produced in only 4 cases, as we advanced our doses of the eight-day isotope more cautiously.

[2] Our standardization of I^{131} has been made by comparing its gamma rays with those from radium standards using a platinum screen cathode counter of known efficiency shielded with 1/4-in. aluminum.

4. The only histologic study as yet available is from a gland removed at autopsy nineteen days after treatment with 260 microcuries per gram of tissue. This shows edema and separation of the cells from the basement membrane, but no fibrosis.

5. Toxic effects of the treatment with the eight-day isotope may be related to an exacerbation of the thyrotoxicosis that sometimes occurs in the first one or two weeks following treatment, during which time the release of stored thyroid hormone may be reflected in the rising blood protein-bound iodine. Because of this, we are now engaged in studying the comparative results with preliminary treatment of severely toxic patients with drugs of the thiouracil series. As for the rare patient without hyperthyroidism who through diagnostic error might receive a dose of 8 to 12 millicuries of I^{131}, we believe that the high excretion of this dose would usually preclude the possibility of its producing myxedema.

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SUMARIO

Tratamiento del Hipertiroidismo con Yodo Radioactivo

Entre 1943 y 1947, 65 enfermos con hipertiroidismo fueron tratados con yodo radioactivo de una semivida de doce horas, I^{130}. Desde agosto, 1946, hasta la fecha otro grupo de 65 pacientes ha sido tratado con el isotopo de ocho días, I^{131}. A base de esos casos, sácanse las siguientes conclusiones:

I^{130}: El yodo radioactivo de semivida de doce horas ha sido empleado eficazmente, por sí solo, en una sola dosis retenida promediando 20 milicuries, o sea 0.45 milicuries por gramo estimado de tiroides, entregándose 90 por ciento de la irradiación en las primeras 36 horas. Se ha producido mixedema. Histológicamente, se han observado fibrosis e hiperplasia regenerativa en tiroides al año y dos años del tratamiento. No se han observado recidivas ni recurrencias del hipertiroidismo. Los efectos tóxicos de esta forma de radioactividad han consistido en: náuseas, febrícula y edema e hiperestesia transitorios del tiroides. No se han notado signos tardíos de efectos contraproducentes. Dosis eficaces, administradas en el segundo y quinto meses del embarazo, no ocasionaron cretinismo u otra patología discernible en los niños, pero no se aconseja la administración a partir del tercer mes de gestación.

I^{131}: El yodo radioactivo de semivida de ocho días resultó también eficaz como único agente terapéutico. En 41 enfermos que respondieron al tratamiento, la dosis retenida media fué de 0.142 milicuries por gramo estimado de tiroides, entregándose 97 por ciento de esta dosis en 30 días. En la mayor parte de los casos la dosis efectiva administrada fué de 8 a 14 milicuries por vía bucal. Sólo se produjo mixedema en 4 casos. No se observaron recidivas. El único estudio histológico realizado reveló edema y desprendimiento de las células de la membrana pavimentosa, pero no fibrosis. Los efectos tóxicos pueden relacionarse con una exacerbación de la tirotoxicosis que ocurre a veces en la primera o segunda semanas consecutivas al tratamiento, época esa en la cual la liberación de la hormona tiroidea retenida puede reflejarse en el alza del yodo combinado con proteína en la sangre.

Clinical Experience in Diagnosis and Treatment of Thyroid Disorders with Radioactive Iodine (Eight-Day Half-Life)

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IT IS WELL KNOWN that the thyroid gland takes up iodine (1). When radioactive isotopes of this element became available, tracer studies were carried out to discover what portion of an administered amount lodged in the gland, and what became of the remainder (2, 3). In this first work, the radioactive iodine was mixed with a relatively large amount of the stable iodine isotope (carrier), which competed with the radioactive form for utilization. It was not possible to administer much radioactive material without at the same time using quantities of stable isotope larger than the individual's normal daily requirement of this element. In this case, thyroid behavior might have been complicated by an iodine effect. Furthermore, with the small amounts of radioactivity used, quantitative measurements *in vivo* were not entirely satisfactory. Later, carrier-free radioactive iodine became available, and its use circumvented these earlier difficulties. With this material, considerable radioactivity is carried by very minute amounts of iodine, so that the quantity of the element administered is much smaller than the normal daily intake. Tracer studies have been carried out with this material in various institutions, to determine uptake and excretion in normal individuals and those suffering from thyroid disorders (4, 5, 6, 13). These investigations showed that in the normal subjects, within twenty-four hours, about 20 per cent of the administered material is in the gland, and most of the rest has been excreted by the kidneys. In toxic goiter, the glandular uptake is two to four times that in the normal.

In view of these findings, it appeared that radioactive iodine might be used to deliver an internal radiation therapy to the hyperactive gland. As the radioactive atoms disintegrate, they emit beta and gamma rays, producing the same type of tissue reaction as x-rays, but with the difference that the irradiation is markedly localized in the gland itself. This is in contrast to the much larger volume of tissue necessarily irradiated when x-rays are used. The amount of radiation delivered into the gland depends on the amount of isotope deposited there, its half-life, and the type of radiation it emits.

Two isotopes of iodine are suitable for attempting this type of therapy: I^{130}, with a half-life of 12.6 hours, and I^{131}, with a half-life of eight days. The latter was not readily produced until recently, but the fomer became available in a few localities about 1943, and two groups in Boston employed it for therapeutic purposes in toxic goiter (7, 8). Results obtained in other clinics have not yet been reported.

Since the release of isotopes from the pile at Oak Ridge, it has been possible for suitably equipped institutions to obtain I^{131}.[2] Accordingly an appraisal of the treatment of toxic goiter with this agent has been undertaken in several hospitals.

The study here reported was begun in October 1946; the material is presented as a preliminary report.

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[1] From the Departments of Medicine and Radiology, Columbia University, College of Physicians and Surgeons, and the Presbyterian Hospital, New York, with the aid of grants from the Committee on Therapeutic Research, Council on Pharmacy and Chemistry, American Medical Association, and the Lilla Babbitt Hyde Foundation. Presented at the Thirty-third Annual Meeting of the Radiological Society of North America, Boston, Mass., Nov. 30–Dec. 5, 1947.

[2] I^{131} is produced by bombarding tellurium^{130} with neutrons. The resulting Te^{131} is radioactive, with a half-life of twenty-five minutes; it decays into I^{131}, which can then be chemically separated from its parent.

PROCEDURE

At the start of the work an adequate basis for dosage planning was lacking. Standards for determining the millicurie activity of the radioactive material were not established. Inter-institutional comparisons showed discrepancies of the order of 100 per cent among the activities characterized as "one millicurie" in various laboratories. This was not due to any lack of exactness in the physical definition of the millicurie, but to variations in the practical application of instruments and to the lack of an authoritative control standardization bureau. At the College of Physicians and Surgeons, Geiger counters were standardized according to the millicurie established by L. D. Marinelli by ionization chamber measurements at Memorial Hospital.[3]

Decision as to the dosage to be used for therapy involved taking into account glandular uptake and subsequent gradual loss from the gland, as well as the amount of energy released by the radioactive atoms. Calculations were made as follows: Theoretical considerations show that if a relatively small organ has a uniform concentration of one microcurie of I^{131} per gram, and the isotope remains there for total decay, the tissue will receive a radiation dose of about 160 equivalent roentgens[4] (9). In the case of the toxic thyroid gland, the iodine gradually leaves the organ at such a rate that the dose is reduced to about 120 e.r. (*loc. cit.*). Cases successfully treated in the earlier series mentioned above, with the 12.6-hour isotope, appear to have received 2,000 to 4,000 e.r. (7, 8). When radiation is delivered more slowly, a larger total number of roentgens is necessary to produce the same result;

[3] Marinelli's measurements have been accepted as standard by all the hospitals which use radioactive iodine in New York City, pending the establishment of a reference unit by the Bureau of Standards.

[4] The roentgen is a unit for x-rays and gamma rays; it is not at present defined for beta rays. When these are used, dose is expressed in "equivalent roentgens." The equivalent roentgen is that amount of beta radiation which, under equilibrium conditions, releases in one gram of air as much energy as one roentgen of gamma rays. The unit is abbreviated "e.r."

Fig. 1. Plasticine models for aid in estimating size of thyroid gland.

accordingly, for the eight-day isotope it was felt that a dose of the order of 3,000 to 5,000 e.r. should be objective. Assuming a 60-gram thyroid gland, an uptake of 50 per cent of the administered material, and a gradual loss by elimination from the gland, a dose of about 4 millicuries would be calculated to deliver this radiation. Treatments were started with this as the standard amount administered for all cases, regardless of the size of the gland. It was realized that, because of differences in gland size and in radioactive uptake, there would be considerable variation in the actual radiation administered, so that an appraisal of clinical response to various doses could be made.

In the early cases a tracer dose was not always given in advance of therapy; later this became routine, in order to obtain an idea of the uptake and thus adjust the dose. The radioactive material was given by mouth, in water solution, the iodine being carrier-free (*i.e.*, all radioactive). The 4 millicurie dose contained only about 0.03 microgram of iodine; this is well below the normal daily intake of the element.

Just prior to treatment, the size of the gland was estimated. To aid in this, a series of plasticine models were constructed, as shown in Figure 1, and their volumes determined by liquid displacement. They were, for the normal gland, 25 c.c., and for the four stages of enlargement,

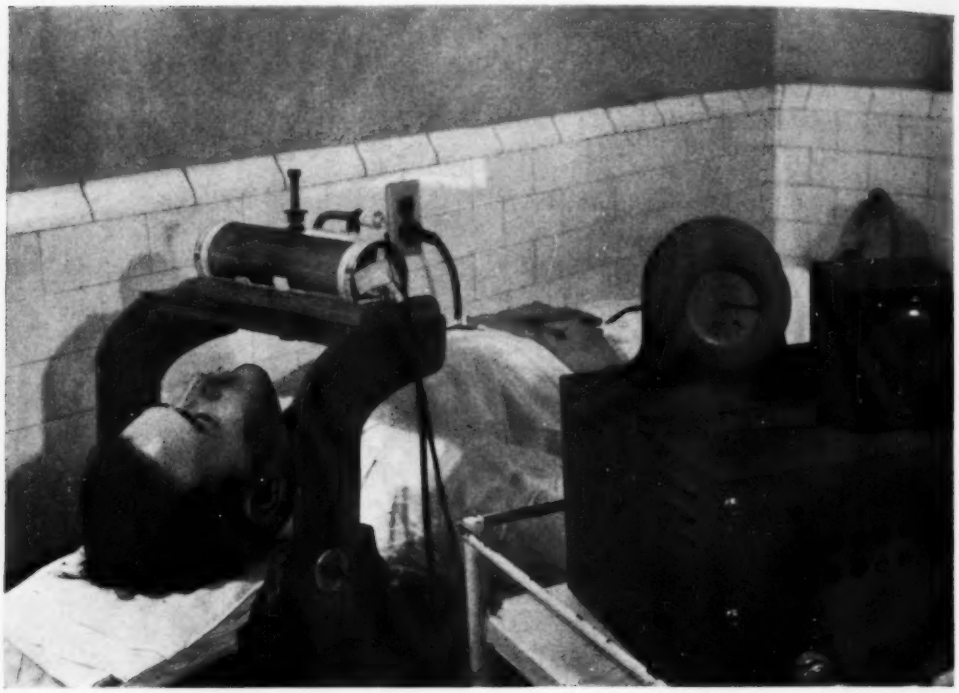

Fig. 2. Patient being measured for radioactive iodine uptake.

35, 50, 70, and 100 c.c. By palpation, it is possible to assign a particular patient's gland to one of these groups, or to a value halfway between two, with full realization of the lack of accuracy of the method.

The radioiodine uptake by the gland was measured at different times after ingestion. The patient was placed in a frame, as shown in Figure 2, so that the skin over the isthmus of the thyroid was always 15 cm. from the Geiger counter. In the first 20 patients, uptake was followed minute by minute from the time of administration for about forty minutes, then at three, six, twenty-four, and forty-eight hours, and weekly thereafter as long as there was measurable activity. In the rest of the series, the early counts were omitted; the record was begun at twenty-four hours and carried on as before, as long as possible. By means of these measurements over several weeks, the "biological half-life" of the iodine in the gland was determined. This is the rate of decrease of radioactivity due to a combination of physical decay and physiological elimination, and must be known for dosage calculation.

Urinary excretion was followed for twenty-four or forty-eight hours wherever possible.

Dosage was calculated for all treatments according to the formula:

$$\text{Equivalent roentgens} = \frac{\text{microcuries administered} \times \%\ \text{uptake}}{\text{grams thyroid weight}} \times \frac{\text{biol. half-life}}{8.0} \times 160$$

In addition to the cases treated for toxic goiter, tracer studies of uptake and excretion have been carried out in a considerable number of individuals. These will be reported in a separate paper, but certain relevant data will be included here.

RESULTS: TRACER STUDIES

The presence of iodine in the thyroid

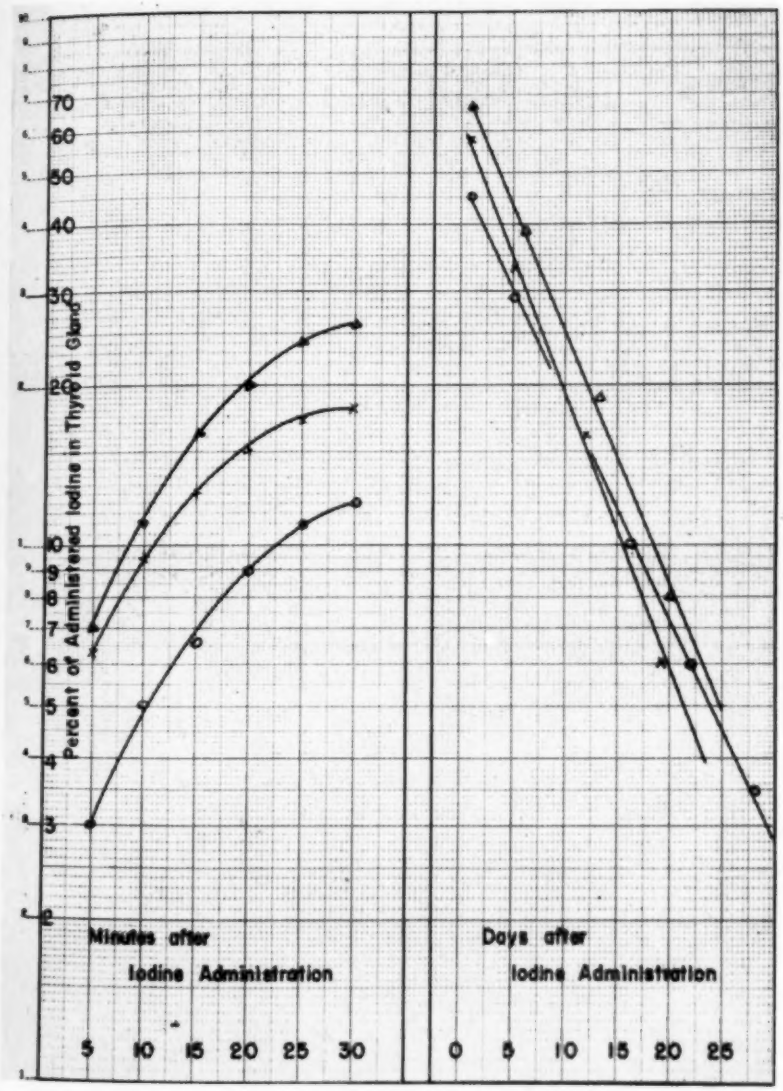

Fig. 3. Curves showing uptake of radioactive iodine by the thyroid gland, and its later disappearance therefrom, in three patients with hyperthyroidism. (Note change in time scale.) The decrease in iodine content shown in the second part of the figure is due to the combined effects of radioactive decay and of iodine excretion by the gland.

gland has been demonstrated within two or three minutes after ingestion; in some cases the amount in the gland increased very rapidly, in others more slowly. Figure 3 shows data for three cases. (Note the change in the time scale after the first rapid rise.) It is evident that there is considerable variation among individuals. However, these immediate uptake curves appear to be susceptible of no direct clinical interpretation. From the later part of the curve, as mentioned above, the biological half-life is determined. This varies from four to seven days, the average being about six days.

The uptake of radioiodine by the thyroid

TABLE I: UPTAKE OF RADIOIODINE BY THYROID GLAND AND URINARY EXCRETION OF THE ISOTOPE IN TRACER STUDIES*

Type of Case	Per Cent in Gland at 24 Hours			Per Cent Excreted in 24 Hours			Number of Cases
	Maximum	Minimum	Average	Maximum	Minimum	Average	
A. Patients without known thyroid disorder	34	11	21	76	28	52	30
B. Patients with known thyroid disorder							
Toxic goiter							
Diffuse	76	44	65	27	6	17	28
Nodular	67	33	52	..	10	..	7
Hyperophthalmic	60	54	58	25	18	22	4
Non-toxic nodular goiter	24	15	19	Data incomplete			3
Hypothyroidism	4	1	3	62	48	55	5

* Tracer doses were 40 to 100 μc. of I^{131} administered by mouth in the form of soluble iodide, carrier free. Uptake measurements *in vivo*, Geiger counter 15 cm. from skin over thyroid.

gland and its urinary excretion at twenty-four hours after administration have been summarized for a series of tracer and therapy patients in Table I. In the individual case, the sum of thyroid and urinary I^{131} at the twenty-four-hour period never represents 100 per cent of the administered material, but varies from 70 to 85 per cent of this, the remainder being distributed in small concentrations in the blood and certain other organs. Thus urinary output is qualitatively in inverse proportion to thyroid uptake, though not an exact quantitative reflection of it.

Both uptake and excretion are more rapid in the hyperthyroid than in the normal subject. This might be expected, as a result of the increased need for iodine and the increased circulation rate and renal clearance which prevail in this disorder.

In 30 individuals without known thyroid disorder, the gland uptake at twenty-four hours varied from 11 to 34 per cent of an administered tracer dose of 50 to 75 microcuries of radioactive iodine. In only one instance was uptake above 30 per cent, and in only 2 below 15 per cent. In general, it is felt that from 15 to 30 per cent should be accepted as the normal range. In 28 cases of toxic diffuse goiter, uptake was from 44 to 76 per cent, which is well above the normal range in all instances. In 5 hypothyroid patients, uptake was from 1 to 4 per cent.

Iodine uptake is largely inhibited by the previous administration of iodine, as Lugol's solution, iodized salt, or gallbladder dye, and it may be disproportionately high immediately after iodine lack. One must watch for these sources of error.

In a series of 35 normal and hyperthyroid patients given radioiodine, the urine was collected in two parts, one for the first six hours and the other for the remaining eighteen. In the 13 cases of hyperthyroidism, the average radioiodine excretion in the first six hours was 15 per cent; in the remaining eighteen hours, 7 per cent. In only two instances was there as much in the eighteen-hour as in the six-hour period. In the 22 individuals without hyperthyroidism, the first six-hour excretion averaged 22 per cent, the next eighteen-hour, 33 per cent. In all but 7 instances the excretion in the second period exceeded that in the first. As suggested above, the high early excretion by the toxic goiter group is probably due to increased renal clearance.

THERAPEUTIC STUDIES

(*a*) *Type of Case:* Up to the present time, 40 cases of unquestioned toxic goiter, given 47 treatments with I^{131}, have been followed long enough to permit some evaluation of the results of therapy. The follow-up period has ranged from four months to more than a year. The diagnostic routine undergone in the thyroid clinic has been outlined elsewhere (10), but now includes radioactive iodine tracer

TABLE IIA: RELATION OF SUCCESS OR FAILURE WITH I^{131} TREATMENT AND DOSE IN MICROCURIES OF I^{131} ADMINISTERED PER GRAM OF ESTIMATED GLAND WEIGHT

Microcuries Administered per Gram	Number of Treatments*		
	Success	Failure	Total
>250	1	0	1
200–250	2	0	2
150–199	3	0	3
100–149	7	2	9
50–99	12	8	20
<50	3†	6	9

* Data not available in 3 instances.
† These were all second treatments after failure to respond satisfactorily to the first treatment.

studies in the event of uncertainty. Fourteen of the 40 patients were men, 26 women. Ages ranged from twenty-three to fifty-seven. Eighteen of the cases were primary toxic goiter not treated by any means before radioiodine therapy, whereas 22 cases were recurrent after operation and had received antithyroid drug therapy, from one to two years, without remission on stopping treatment, in most instances. These latter cases had frequently also received x-ray treatment before being given radioiodine. With a single exception, the cases were all toxic diffuse goiter. To avoid an irrevocable step, no true hyperophthalmic goiter was treated. The recurrent and primary cases will be considered together in the analysis of results, since no significant difference in response between the two groups has been noted.

The basal metabolic rate prior to treatment ranged from +23 to +76 per cent, about half being above 40 per cent. The height of the metabolism rate appears to be related to the success or failure of the therapy as given. This will be discussed later. Gland size was estimated as described above. Sixteen of the 40 patients had glands estimated to weigh 70 gm. or more prior to therapy. The rest varied down to less than normal size in some of the recurrent group. Again success or failure of treatment appears related to this factor.

(*b*) *Dosage and Clinical Response:* (*1*) *Millicuries:* All cases in this series received between 3 and 4 mc. regardless of toxicity of the goiter or gland size; 12 treatments were given with 3 to 3.8 mc., and 35 with 4 mc. There were 3 failures and 9 successes in the group receiving from 3 to 3.8 mc. There were 14 failures and 21 successes in the 35 cases which received 4 mc. *In toto,* there were 13 failures in 40 patients given a single dose of 3 to 4 mc. of I^{131}. Seven of these cases were given second treatments, with 4 additional failures. (One of the 4 patients receiving a second treatment has been lost to follow-up but is included as a failure.) Thus 34 of 40 patients were treated once, or if necessary twice, and have been followed for four months or more since treatment. Thirty of these 34 have been finally put into remission, a case rate of 88 per cent. The other 6 cases of failure have been retreated too recently for appraisal and these retreatments have not been included in this report. On the basis of treatments given, however, there are 17 failures in 47 treatments, or a treatment success rate of 64 per cent.

TABLE IIB: RELATION OF SUCCESS OR FAILURE WITH I^{131} TREATMENT AND DOSE IN MICROCURIES OF I^{131} RETAINED IN GLAND PER GRAM OF ESTIMATED GLAND WEIGHT

Microcuries Retained per Gram	Number of Treatments*		
	Success	Failure	Total
>100	3	0	3
75–100	3	0	3
50–74	7	1	8
25–49	11	8	19
<25	4†	7	11

* Data not available in 3 instances.
† Three of these were second treatments after failure to respond satisfactorily to the first treatment.

(*2*) *Microcuries per Gram of Estimated Gland Weight:* A standard dosage of 3 or 4 mc. does not take into account dosage per gram of gland tissue. It is obvious that the larger glands receive much less actual radiation under this condition. Therefore, estimates of gland weight must be made in order to permit any determination of administered dosage. This was done as described earlier; while the method is admittedly inaccurate, it serves a useful purpose. On this basis, the calculated number of microcuries administered per

TABLE III: RELATION OF SUCCESS OR FAILURE WITH I^{131} TREATMENT AND CALCULATED DOSAGE TO THYROID GLAND IN EQUIVALENT ROENTGENS

Dose in e.r.	Number of Treatments*		
	Success	Failure	Total
10,000	4	0	4
9–10,000	0	0	0
8–9,000	3	0	3
7–8,000	2	1	3
6–7,000	3	1	4
5–6,000	3	1	4
4–5,000	2	2	4
3–4,000	5	8	13
2–3,000	3	1	4
1–2,000	3†	2	5

* Data not available in 3 instances.
† These three were second treatments after insufficient response to the first one.

gram of gland tissue is related to result of treatment in Table IIA. No failures occurred in the 6 treatments where the dosage was 150 μc. or more per estimated gram of gland, and only 2 in 9 cases receiving between 100 and 150 μc. per gram. With less than 100 μc. per gram, the successes and failures were equally divided. It is of interest that the 4 cases of transient hypothyroidism occurring in the series received less than 150 μc. per gram.

The actual irradiation is the result not of the number of μc administered per gram of gland, but of μc. retained there. Accordingly, for each patient, the value for μc. per gram administered was multiplied by the percentage uptake at twenty-four hours to determine the μc. per gram retained. The results are given in Table IIB. It is of interest that the values in this table are almost exactly half those in Table IIA. Thus, on the average, the uptake was 50 per cent, although it varied considerably in the individual cases. There were no failures in cases with retention of more than 75 μc. per gram, and only one with a retained dose of more than 50 μc. per gram. On the other hand, only one case responded satisfactorily to a first dose of less than 25 μc. per gram.

(3) *Equivalent Roentgens:* The actual administered dose of radiation, in terms of equivalent roentgens, depends not only on the uptake of I^{131} by the gland, but also on its subsequent elimination therefrom, according to the formula given earlier in this paper. These doses, and their results, are shown in Table III. They ranged from 1,000 to more than 10,000 e.r. No failures occurred in the 7 cases receiving 8,000 e.r. or more, and only 3 in the 11 cases receiving from 5,000 to 8,000 e.r. With less than 5,000 e.r., there were 13 failures and 13 successes; of the successes, 3 followed second treatments after the first had failed. The 4 instances of transient hypothyroidism occurred with doses of 2,900, 6,900, 7,400, and 8,600 e.r.

FURTHER ANALYSIS OF FAILURE OF TREATMENT

A more detailed analysis has been made of the several variables which might influence the ultimate dosage from radioiodine received by the gland, and hence the success or failure of treatment. The factors influencing dosage are the weight of the gland, the percentage of the radioiodine retained there, and its rate of release. In addition, the effect of basal metabolic rate may be significant. It is not satisfactory to consider these factors separately; they are too closely interrelated. However, an attempt is made to analyze their importance.

(*a*) *Basal Metabolism Rate:* The higher the basal metabolic rate, apparently the higher the failure rate. Among 17 cases with basal levels of 50 per cent or greater at the time of treatment, there were 11 failures and 6 successes. Among 29 cases with initial basals below 50 per cent, there were 23 successes and 6 failures. One initial basal record is lost.

It is a question, however, whether the failure is the result of the high basal metabolic rate *per se* or whether these higher rates are associated with larger glands, and hence with lower actual doses in this series. Table IV indicates that this is probably the case. Only 3 of 18 glands of less than 50 gm. weight were associated with basal metabolic rates above 50 per cent, while 14 of 26 larger glands had basals of this magnitude.

In Table V the relation of basal metabolic rate to success or failure of treatment

TABLE IV: RELATION BETWEEN ESTIMATED SIZE OF GLAND AND BASAL METABOLIC RATE

BMR (per cent)	Estimated Weight, in Grams*					Total
	<25	25–34	35–49	50–74	75–100	
70–80	0	0	0	1	1	2
60–69	0	0	0	4	2	6
50–59	0	1	2	4	2	9
40–49	0	2	2	3	0	7
30–39	2	1	2	5	0	10
20–29	1	1	4	3	1	10

* Data not available in 3 instances.

TABLE V: RELATION OF SUCCESS OR FAILURE WITH I^{131} TREATMENT TO INITIAL GLAND SIZE AND BASAL METABOLIC RATE

BMR (per cent)	Number of Treatments*					
	Success		Failure		Total	
	<50 gm.	50–100 gm.	<50 gm.	50–100 gm.	<50 gm.	50–100 gm.
70–80	0	0	0	2	0	2
60–69	0	2	0	4	0	6
50–59	1	3	2	3	3	6
40–49	4	2	0	1	4	3
30–39	5	2	0	3	5	5
20–29	6	3	0	1	6	4

* Data not available in 3 instances.

is shown for the two size classifications. This appears to have more meaning than an unqualified relation of basal metabolism to result, in a series receiving such divergent doses. It is now seen that, of the 11 failures in 17 treatments with basal levels greater than 50 per cent, referred to above, 9 represented glands of more than 50 gm. weight. Of the 6 failures in the group having basal levels below 50 per cent, 5 represented glands heavier than 50 gm.

(*b*) *Size of Gland:* In a series of patients receiving the same amount of I^{131}, it is evident that, other things being equal, those with the larger glands received smaller doses of radiation and therefore would not be expected to show as good results. In this series, the larger glands have been associated with higher basal metabolic rates and hence are presumably more actively functioning, which may be a possible further factor in resistance to therapy. Until a larger series is available with larger glands receiving the same number of roentgens or μc per gram as the smaller, it is not possible to evaluate effect of gland size *per se*.

(*c*) *Uptake of Radioiodine:* It might be expected that the individuals showing higher percentage uptake would present a larger number of successes of treatment, since in this series this implies a higher radiation dose, and this is apparently the situation. Among 9 cases with uptakes of over 60 per cent, there was only 1 failure, and this in a very large gland (Table VI). In the medium uptake group success and failure are about equally divided; the two successes in the very low uptake group were second treatments, after incomplete response to the first.

There appears to be no definite relationship between the basal metabolic rate and the percentage uptake in the gland at twenty-four hours (Table VII). It might be suggested that in the individuals with very high basal metabolic rates, a very rapid early uptake and subsequent release of material might result in a lower reading at twenty-four hours than would have been found earlier. In the first group of patients followed at one, three, and six hours, one such case was observed. If this were generally true, however, it would follow that the biological half-life would be shorter for patients with high basal rates

TABLE VI: RELATION OF SUCCESS OR FAILURE WITH I^{131} TREATMENT TO GLAND SIZE AND I^{131} UPTAKE AT TWENTY-FOUR HOURS

Per Cent Uptake	Number of Treatments*					
	Success		Failure		Total	
	<50 gm.	50–100 gm.	<50 gm.	50–100 gm.	<50 gm.	50–100 gm.
70–80	1	0	0	0	1	0
60–69	4	3	0	1	4	4
50–59	4	7	1	8	5	15
40–49	5	1	1	1	6	2
30–39	0	1	0	3	0	4
20–29	0	0	0	1	0	1
10–19	2†	0	0	0	2	0

* Data not available in 3 instances.
† These were second treatments after insufficient response to the first.

TABLE VII: RELATION OF BASAL METABOLIC RATE TO GLAND SIZE AND PER CENT UPTAKE OF I^{131} AT TWENTY-FOUR HOURS

Per Cent Uptake	Basal Metabolic Rate*					
	<30%		30–59%		>60%	
	<50 gm.	50–100 gm.	<50 gm.	50–100 gm.	<50 gm.	50–100 gm.
70–80	1	0	0	0	0	0
60–69	3	0	2	2	0	0
50–59	1	1	3	6	0	4
40–49	0	0	6	2	0	0
30–39	1	1	0	3	0	1
20–29	0	0	0	3	0	1
10–19	1	1	1	0	0	0

* Data not available in 3 instances.

TABLE VIII: RELATION BETWEEN BIOLOGICAL HALF-LIFE AND BASAL METABOLIC RATE

Biological Half-Life (days)	Basal Metabolic Rate							
	30%		30–49%		50–69%		70%	
	S*	F*	S	F	S	F	S	F
<5	2	0	3	0	1	0	0	0
5–5.9	4	1	5	0	4	1	0	1
6–6.9	3	0	6	1	0	3	0	0
7 or more	1	0	0	3	1	5	0	1

* S. Success. F. Failure.

but, as seen in Table VIII, this is not the case. In fact, there appears to be no significant relation between the two.

In Figure 4 an attempt is made to visualize the importance of the various factors discussed above, showing for each case the gland size, basal metabolic rate, and dose in equivalent roentgens. The upper half of the figure deals with the successes, the lower with the failures. As might be expected, the failures show a concentration in the low dosage region, with large glands and high basals. Interestingly enough, there are also some successes in this group, but more occur with larger doses, which in this series implies smaller glands. It will be important to see corresponding charts in a later series, when larger glands have received correspondingly large doses.

TIME NECESSARY FOR RETURN OF BASAL METABOLIC RATE TO NORMAL

Although in a few successfully treated cases there was a return of the basal metabolic rate to normal in less than two months, most of the cases were not in remission until the end of the second or

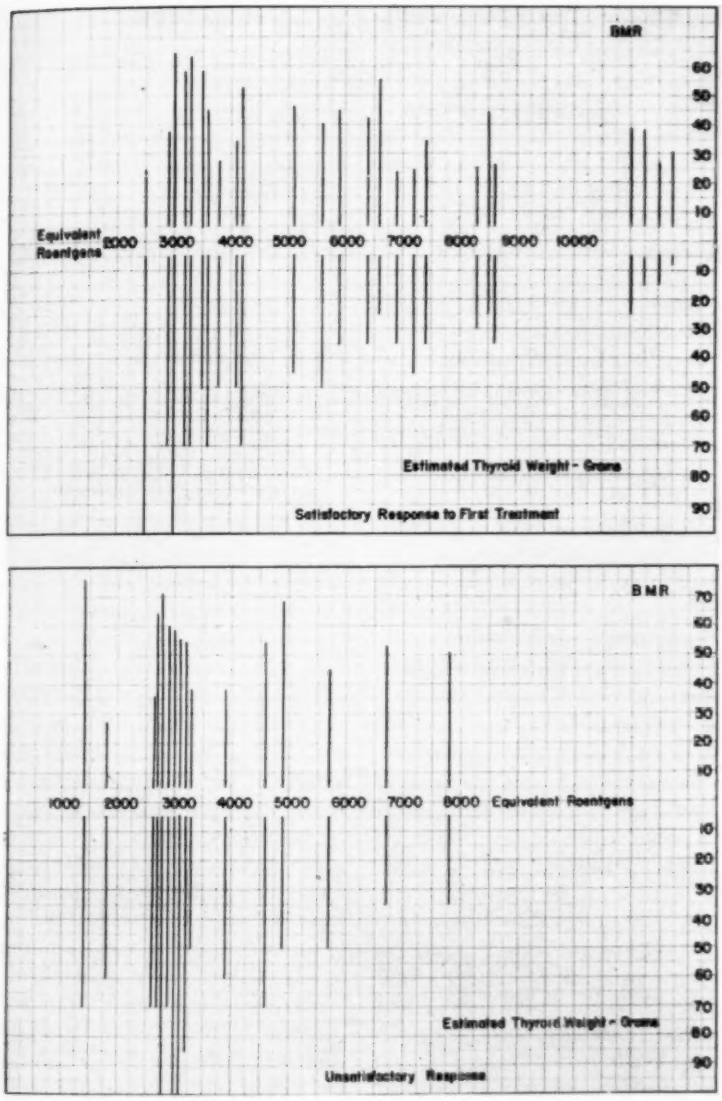

Fig. 4. Chart showing radiation dosage, basal metabolic rate (BMR), and gland size for each individual case. Upper part, successful treatments; lower, unsuccessful. Each patient is represented by two lines, starting at the administered dose in equivalent roentgens. The line extending upward indicates the basal metabolic rate; the one extending downward, the estimated thyroid weight.

middle of the third month. A few required even longer (Table IX).

COMPLICATIONS

The incidence of complications resulting from this therapy is not high.

(*a*) *Hypothyroidism:* Four instances of transient hypothyroidism occurred with I^{131} doses of 3 to 4 mc., radiation doses of 2,900, 6,900, 7,400, and 8,600 e.r. The symptoms and signs of hypothyroidism were noted in the third to fourth month after the ingestion of the iodine, and cleared within the space of a month, with one ex-

TABLE IX: TIME ELAPSING AFTER RADIOIODINE THERAPY BEFORE RETURN OF BASAL METABOLIC RATE TO NORMAL

Months between Treatment and Establishment of Normal BMR	Number of Cases*
0–1	2
1–2	12
2–3	10
3–4	5

* Data not available in 1 instance.

ception, which required somewhat longer. Basal metabolic rate depression and serum cholesterol rise were noted during the hypothyroid period, with return to normal limits on recovery.

(*b*) *Sore Throat and Cough:* A persistent sensation of a head cold or sore throat occurred in 6 instances with hacking cough, and in one other cough alone, following I^{131} treatment, without adequate evidence of an upper respiratory infection to account for the symptoms. This complication appeared several weeks after treatment, and subsided four to six weeks later. These patients received doses between 4,000 and 6,000 e.r.

(*c*) *Tender Gland:* Marked tenderness of the thyroid gland to palpation was noted in 2 cases, subsiding after several months. The gland became indurated; this characteristic was observed in many cases without associated tenderness.

(*d*) *Flare-up of Toxicity:* Three instances of increased toxicity in the month following therapy were noted. This flare-up brought the basal metabolic rate about 15 per cent higher than before therapy, and was sufficient to create alarm concerning the patient's status, though fortunately cardiac failure or thyroid storm was not precipitated in any instance. These patients received from 3,500 to 6,000 e.r. They all failed to go into remission following their first course of therapy.

(*e*) *Radiation sickness* was not noted.

(*f*) *Intercurrent Pregnancy:* Two patients were unwittingly treated in the first two months of pregnancy. No apparent harm to patient or fetus has resulted so far. One mother has been delivered of an apparently normal child.

REDUCTION IN GLAND SIZE

In most cases, the glands were reduced to within normal limits, or less, by three months following therapy, when remission was obtained. In the instances of failure of therapy, gland size usually was somewhat reduced, although not to normal limits.

RADIATION HAZARDS

The possibility of late radiation damage leading to malignant change following I^{131} therapy has been suggested. In an attempt to discover whether such changes had ever been observed following x-ray therapy, in either a normal or a hyperthyroid gland, a questionnaire was sent to a group of radiologists and thyroid specialists. Over 100 replies were received, of which a detailed analysis will be published elsewhere. In the whole group of answers, three cases were reported in which cancer appeared in a gland irradiated some years earlier for toxic diffuse goiter; in none of these was the radiation dose probably more than 3,000 r. At least one case was reported in which carcinoma arose in a nonnodular hyperthyroid gland which had received no radiation. It appears that the amount of radiation received by the gland in x-ray therapy is not enough to make late malignant change a hazard to be considered. However, the radiation dosage with I^{131} may be considerably greater in localized regions (11), and the possibility of the danger cannot be dismissed. The general feeling of those replying to the questionnaire was that this type of therapy should be carried out for the present as an experimental procedure, in clinics properly equipped to study and follow the cases, but should not be generally employed for some time, until more data are available.

Dangers to individuals other than the patient, from the effects of radiation, must be mentioned. The safety of the laboratory workers who receive, dilute, measure, apportion, and administer the material, is the responsibility of the health physicist of the institution, and need not be discussed

here. Danger to those attending the patient or to other patients in adjacent beds is negligible, but this should possibly be analyzed.

A patient who has received 4 mc. of I^{131} and retained 75 per cent, or 3 mc., represents the maximum hazard under the present scheme of treatment. Practically none of the beta rays escape from his body. The gamma ray intensity from an unfiltered source of 1 mc. at a distance of 1 cm. is 2.65 r per hour (9). At a distance of two meters from the patient's thyroid, assuming no absorption of gamma rays in the body, the intensity is 0.00006 r per hour per mc. In the first twenty-four hours, then, the dose at this distance from a patient retaining 3 mc. is about 0.004 r; this daily becomes less with radioactive decay. It is seldom that patients in wards are not separated by at least 2 meters. Since the permissible daily dose is 0.1 r, it is evident that a single such patient in a ward presents no risk, nor do several, if they are at least this widely spaced.

For the nurse or doctor who might spend as much as an hour within a distance of half a meter from the thyroid, the exposure on the first day would not exceed 0.01 r. It is evident that this much time could be spent close to several patients without exceeding the permitted exposure. The iodine which is not concentrated in the thyroid gland is excreted in the urine—most of it, in the hyperthyroid patient, in the first six hours. If these specimens are flushed down the sewer in the normal course of events, where not more than two or three patients per week are being treated the radiation levels in the plumbing will not exceed those generally recommended as within safe limits (12). If larger numbers of patients are treated and kept in one ward or wing of the hospital, special monitoring should be instituted, both for ward safety and for flushable waste.

It is often desired to save twenty-four hour specimens of urine in order to measure the excretion. Such specimens are customarily kept in a service room for the night and delivered to the laboratory once daily. If a patient receiving 4 mc. excreted 50 per cent in the first twenty-four hours, of which half came in the first collection, then a jar containing 1 mc. of I^{131} might remain in the service room for almost twenty-four hours. No one individual would be as near it as one meter for more than eight hours. An attendant actually sitting within 1 meter of it for that total period would receive less than 0.002 r. It is evident that the excretion collections from a few patients would not be a source of danger while they remained in a corner of a service room. If one held in his hand for one minute a full 2-liter jar containing 1 mc. of I^{131} the hand would receive an exposure of the order of 0.01 r.

It appears, therefore, that as long as the number of patients undergoing treatment at one time is small, the danger to other patients or to attendants is negligible.

DISCUSSION AND CONCLUSIONS

Radioactive iodine, half-life eight days, I^{131}, has been used both for the study of normal and disordered thyroid function, with tracer dosage, and for the control of primary and recurrent toxic goiter, with therapeutic dosage of the material.

The tracer studies indicate that the individual without known thyroid disorder has an uptake of radioiodine by the thyroid gland at twenty-four hours which is within a sufficiently narrow range to set limits beyond which thyroid dysfunction can be diagnosed. The normally functioning gland takes up, within the first twenty-four hours after ingestion, between 15 and 30 per cent of a tracer dose of 40 to 100 μc. In toxic goiter the uptake almost always exceeds 40 per cent of the tracer dose, while in hypothyroidism it remains under 10 per cent. The previous use of stable iodine from some other source (*e.g.*, gallbladder dye, iodized salt, or iodine in preparation for operation) decreases radioiodine uptake sharply in the normal and toxic glands. This would cause a serious error in uptake determination and hence must be avoided prior to tracer studies, or to therapeutic administration, where high

uptake is desirable to obtain high radiation effect.

Urinary excretion in the first twenty-four-hour period after radioiodine ingestion has a range of from 40 to 70 per cent in the normals and hypothyroids, and is decreased to from 10 to 40 per cent in the hyperthyroid cases. After the first day, excretion continues at a significant rate only in hypothyroids. The toxic group excretes more of the material in the first six hours than in the following eighteen, probably due to increased renal clearance, whereas this is reversed in the normal subject. The measurement of urinary excretion thus may be used to diagnose toxicity, but is not as reliable a test as is measurement of gland uptake (13).

The therapeutic studies are encouraging. A case remission rate of 88 per cent has been obtained thus far, although the series is too small as yet to draw statistical conclusions. The case success rate is lower than the remission rate for individual treatments; this means that, when the first attempt is inadequate, retreatment may succeed. How often such therapy can be repeated is not yet known; in the present series an arbitrary limit has been set of two courses. The case success rate is especially important in that over half the patients had goiter recurrent after operation, were not desirable surgical risks, and in the main had not come into remission with antithyroid drugs or x-ray therapy.

The present success rate of radioiodine therapy compares well with that of surgery (90 per cent), and surpasses the results of x-ray therapy (80 per cent in selected cases with small glands) and of thiouracil and propyl thiouracil treatment (about 60 per cent in primary goiter, 10 per cent in recurrent goiter) (10). Surgery provides relief in a shorter time than the two or three months usually needed to induce remission with radioiodine, but is open to the objections attendant on operation. Antithyroid drug therapy may take one or two years, without assurance of final success on stopping the drug. However, it has few complications.

Failure of radioiodine therapy in the present series seems related mainly to gland size and height of the basal metabolic rate. Since radiation dosage is determined by the amount of radioiodine deposited in the gland, it is evident that with a limited range of administration, of 3 to 4 mc., the larger glands would be more likely to be underdosed. High basal rates were associated with larger glands more frequently than with small ones. Factors of uptake of radiation by the gland, and its subsequent excretion therefrom (biological half life), must also be taken into account in calculation of actual radiation dosage, on which, in the final analysis, success of therapy must depend. There is also the factor of variable individual response to irradiation, which, at least at present, cannot be evaluated.

Thus the problem in radioiodine therapy of toxic goiter is to select a dosage which will control the toxicity but will not induce permanent gland underfunction and hypothyroidism. The mechanism by which radioiodine produces its effect is probably destruction of a considerable part of the functioning thyroid tissue. For this purpose, administration of about 125 μc. of I^{131} per estimated gram of thyroid weight, or a radiation dose of about 6,000 e.r., appears generally adequate, although obviously this conclusion is tentative until more data are available.

Complications of radioiodine therapy may occur. They include sore throat and cough, tender gland from thyroiditis, flare-up of toxicity, such as has followed x-ray therapy in toxic goiter, and transient hypothyroidism, and are presumably due to radiation effect on the thyroid or neighboring tissues. Permanent hypothyroidism has been reported by others following I^{130} therapy, but has not been seen so far with the doses of I^{131} employed in this series. One complication which may occur unwittingly is the administration of radioiodine for therapy of toxic goiter during early pregnancy, before the latter is realized or declared. In the two such cases in this series, one of which has since come to

term, no immediate ill effect on the fetus has been detected. Possible late results of radiation of this nature have yet to be seen, but they probably will not be serious, in view of the fact that the fetal thyroid is not formed before the third month of gestation (14). Iodine administered to the mother before this stage is rapidly collected in her own gland or is excreted. It is a possibility that the fetus may take up iodine subsequently released into the maternal bloodstream from her previously treated thyroid gland, but this is unlikely to be significant in amount or effect. Treatment of pregnant women, especially after the third month, should be avoided. Finally, malignant exophthalmos has not so far followed radioiodine therapy. If intact thyroid tissue serves to check the development of this complication (a current theory), radiation therapy is contraindicated because it reduces the total mass of tissue. At present, therefore, if this complication appears likely, radioiodine therapy is not suggested.

In this preliminary group, one drawback has been the number of retreatments necessary. This is inevitable in a pilot series, in which the most desirable dosage levels are being sought. It is always necessary to wait at least three months after the initial dose to determine whether the patient is in remission, and then three months more to evaluate the effect of a second treatment. With dosage planned in accordance with the size of the patient's gland, basal metabolism rate, and tracer uptake, the number of retreatments should be considerably less, although some will almost certainly be required. With a patient in cardiac failure (a rare event nowadays), the time element is a serious consideration. Otherwise, even with failure to control the hyperthyroidism completely with one dose, the patient is usually so much improved, and his basal rate so reduced, that he does not suffer unduly by waiting for observation and retreatment.

SUMMARY

1. Radioactive iodine of eight-day half-life, I^{131}, has been used as a tracer and for treatment of toxic goiter.

2. Tracer uptake has diagnostic value when stable iodine has not been given shortly before this procedure and when the diet has not been seriously deficient in iodine. Normal uptake is 15 to 30 per cent of the administered tracer dose of 40 to 100 μc. Anything more than 40 per cent is regarded as definitely indicating hyperthyroidism; anything less than 10 per cent as hypothyroidism.

3. Therapy has been successful in 30 of 34 cases after one or, when necessary, two doses, with 4 failures. Six other treated cases did not respond to one dose, and have not been followed after a second long enough to draw conclusions.

4. The causes of failure in the present series have been analyzed; they appear to be related to inadequate dosage, as a result mainly of large size of the gland. It is possible that an unusually high basal metabolic rate may also contribute to an unsatisfactory result.

5. Complications following radioiodine therapy include sore throat, cough, tender gland, flare-up of toxicity, and transient hypothyroidism. Only a few cases of each have been observed, none of them serious. Malignant change as a sequela in later years following radioiodine treatment is not thought very probable by those who have had long experience with x-ray therapy for hyperthyroidism (response to questionnaire).

6. Radiation hazards to doctors and others associated with patients undergoing this therapy are analyzed; under the present conditions they are unimportant.

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SUMARIO

Observaciones Clínicas Relativas al Diagnóstico y Tratamiento de los Trastornos Tiroideos con Yodo Radioactivo (Semivida de Ocho Días)

El yodo radioactivo de semivida de ocho días, I^{131}, ha sido utilizado como indicador y para el tratamiento del bocio tóxico.

El alza del indicador posee valor diagnóstico si no se ha suministrado yodo estable poco antes del procedimiento y si la alimentación no ha sido netamente deficiente en yodo. El alza normal es de 15 a 30 por ciento de la dosis de 40 a 100 milicuries de indicador administrada. Todo exceso de 40 por ciento se considera como signo bien definido de hipertiroidismo; toda cifra inferior a 10 por ciento como hipotiroidismo.

La terapéutica obtuvo éxito en 30 de 34 casos, con una, o cuando fué menester, dos dosis, habiendo 4 fracasos. Otros seis casos tratados no respondieron a una dosis y no han sido observados tiempo suficiente después de la segunda dosis para sacar conclusiones.

Analizadas las causas de fracaso en la serie actual, parecen relacionarse con una posología inadecuada, debido principalmente al gran tamaño de la glándula. Es posible que un metabolismo basal sumamente alto pueda también contribuir a la obtención de un resultado poco satisfactorio.

Las complicaciones consecutivas a la radioyodoterapia comprenden: angina, tos, hiperestesia tiroidea, exacerbación de la toxicidad e hipotiroidismo transitorio. Los casos observados de cada una de ellas han sido pocos, y ninguno resultó grave. Los que han tenido mucha experiencia con la roentgenoterapia en el hipertiroidismo no consideran muy probable la aparición de malignidad como secuela de la radioyodoterapia en años subsiguientes.

Analizados los riesgos que entraña la radiación para los médicos y otros que rodean a los enfermos que reciben esta terapéutica, no revisten importancia en las condiciones actuales.

DISCUSSION

(Papers by Skanse and Rawson; Frantz, Quimby, and Evans; Marinelli, Trunnell, Hill, and Foote; Chapman; Werner, Quimby, and Schmidt)

Edwin Astwood, M.D. (Boston, Mass.): I am sure all of us have enjoyed this symposium and are grateful to Dr. Quimby for arranging such interesting papers. It is quite apparent to all of us who have listened that radioactive iodine has a bright future both as a tracer substance for studying the thyroid, and as a therapeutic agent. As a tracer it gives us something which has never

been available before, not only in experimental studies but also for diagnosis. As a therapeutic agent, one gets the impression that there is more hope that it will be effective in the treatment of Graves' disease than in the treatment of thyroid carcinoma.

One is struck by the wide range of dosage necessary to achieve a remission in Graves' disease. Dr. Werner spoke of 3 to 4 millicuries per patient, whereas Dr. Chapman used considerably larger quantities. This discrepancy is magnified when one considers the difficulties in standardization. Fortunately, in New York, a millicurie is pretty well standardized and everyone uses the same unit, but so far this uniformity has not spread to Boston. Dr. Quimby kindly sent us a sample which was standardized by Mr. Marinelli. This had an activity 20 to 50 per cent less per microcurie than that stated by Oak Ridge, whereas I believe the standard used at the Massachusetts Institute of Technology and employed by Dr. Chapman is still less. So that the material from Oak Ridge would be approximately double the stated activity by Dr. Chapman's standards.

We hear of others giving dosages of 10 to 15 millicuries on an Oak Ridge basis, which would then correspond to 20 or more millicuries per patient. There is, thus, a wide variation in the minimal effective dose in different patients.

This raises a question as to why the treatment should cure Graves' disease. That same question, of course, has never been answered in the case of total thyroidectomy and in the case of treatment by antithyroid drugs. In both forms of treatment, however, a large percentage of cases are apparently cured even though the fundamental disorder has not in any way been attacked. Both forms of therapy have shown some 10 to 15 per cent of cases that persistently relapse regardless of treatment and I think the cases presented by both Dr. Chapman and Dr. Werner this morning were ones which had already displayed this propensity. Consequently, the cards were stacked against them in the first place, so that the success which they have reported is probably minimal. That is, if they had had unselected cases, which had not received any other form of treatment, the remission rate would have been higher.

The question arises, too, whether these small doses may not have produced a transient metabolic disorder in the thyroid without destroying it, and recovery from the hyperthyroidism took place during the interval when the thyroid's function was thus temporarily disturbed. Recovery following antithyroid therapy apparently is unrelated to any permanent change caused by the drug in the thyroid. Presumably, the artificially induced remission permits spontaneous recovery. Perhaps something similar happens with the small dose treatment with radioactive iodine.

I would like to ask Dr. Frantz and Mr. Marinelli if they will briefly cite for us the side effects noted when very large doses have been given for the treatment of thyroid carcinoma. Apparently huge doses can be given without disastrous results, and that fact alone I think should be quite consoling to those who use this form of treatment for Graves' disease in very much smaller doses.

Finally, I rather look forward to the time when a great number of sections are available showing the histological changes in the gland as remission is brought about by this treatment.

Kenneth E. Corrigan, Ph.D. (Detroit, Mich.): It is a pleasure to be invited to discuss this very interesting group of papers, each presented by an outstanding authority in his own field and each author representing a team. I think that is probably the most significant point of all; this new work that we are engaged in at the present time is strictly a matter of teamwork. It is impossible to make it go without a radiologist, without a physicist, without other assistants, and, most important of all, without interchange of information and balance of ideas in units and standards between various institutions.

The matter of units has taken up much of the time of some of us throughout this week, and I have been asked by the essayists to mention particularly the fact that a millicurie may not be what it appears; in fact, I am informed by the sources directly that 7 Chapman units are equal to 4 Quimby millicuries, approximately.

It also should be remembered that, due to a complete misunderstanding of the size and the significance of the millicurie, one author inflicted upon the literature a serious error some years ago when he put a sample of radioactive iodine into a sealed tube, measured its gamma ray output, balanced that against a millicurie of radon and called it a millicurie of radioactive iodine. Actually, it was something quite different. However, this is a problem that will resolve itself and we can only ask the clinicians to bear with us for a while until we get some more work done and get these minor difficulties settled.

The curie is probably the ideal unit for the handling of all radioactive substances. It is a unit which lends itself to practical use; it is a unit that has dimensions that fit our needs; it is a unit which divides into subdivisions exactly as the ampere does into milliamperes and microamperes. It is necessary for us to learn just one thing more to understand what the curie and its divisions mean; that is, that the curie is not a quantity of gamma ray, but is a quantity of radioactive substance which at zero time is disintegrating at 3.7×10^{10} disintegrations per second. The amount of energy that it will produce will vary, one isotope from another, which is not different than saying that the physiological effects of various drugs vary one from another. You don't ex-

pect a gram of just anything to have the same result as a gram of something else.

We always get into difficulties with the roentgen, and yet the roentgen is still good. After many years of hard work, we have established the roentgen as the unit of x-ray and gamma ray and we are now learning to extend this unit to things about which we know little. There is no reason why this extension cannot be made, but again it will require some work, and to do work usually requires time.

The discrepancies which appear in these papers, I would like to point out, are very much more apparent than real. The differences in dosage can be explained fairly easily. Where radioactive iodine is given in the presence of an appreciable chemical quantity of inactive iodine, the absorption and the retention are very different from that to be expected where the radioactive iodine is given carrier-free. This accounts for a good many of the discrepancies in these papers, where cyclotron iodine made from iodine or cyclotron iodine made from tellurium is compared to radioactive iodine from the pile.

The effects of many different things have been tried in connection with radioactive iodine. It is certainly true that some of the antithyroid drugs, propyl thiouracil particularly, can be used to cut down the dose requirements by increasing the retention in the gland. I notice, also, since I have been out here, that in comparing data with the Memorial group and the Columbia group, and so on, there seems to be a real geographic discrepancy. In the Midwest it is well known that the population is iodine-starved. The iodine concentration of the earth and water is low and there was a very high goiter incidence until recent years, when it has been kept under control due to medical study. Apparently the iodine saturation of the population in the Midwest area is such that when they receive a small trace of radioactive iodine, amounting to a fraction of a microgram, the retention of the radioactive substance is on the average higher than it would be for the same type of patient on the East Coast. This may prove to be a very interesting fact in itself. We have a large number to compare. I think the comparison is valid.

One thing that made my hair stand on end just a little was Dr. Chapman's reference to the administration of radioactive iodine to a pregnant human being, because this is an established method in our laboratory for producing cretin rats and cretinism in other animals.

One thing that might be of slight interest is the mention that has been made of sudden appearance of a toxic state after the administration of therapeutic doses of radioactive iodine in Graves' disease. Just as a little technical trick, this can sometimes be anticipated by taking Geiger-counter readings on the soft tissue of the body, particularly the muscles of the thigh. Before the toxic state will actually develop to the point where the clinical man will be excited about it, the thyroid will secrete enough of its hormone containing the radioactive iodine to definitely raise the blood level and raise the counting rate on the soft tissue remote from the thyroid.

I particularly enjoyed all of these papers. Dr. Rawson, whose work I have had occasion to admire for a long time, has shown us the great advances that we can expect to see in the knowledge of thyroid physiology in the next few years. Dr. Quimby, as usual, has given us an excellent paper with Dr. Werner; and Dr. Frantz is one that I always enjoy listening to, a person with a truly analytical mind who presents things beautifully. Dr. Chapman I have never listened to before, but I shall endeavor to do so in the future.

In closing, I would like to point out that, while these authors—I did not mean to forget Mr. Marinelli—have somewhat stressed the future of this thing, I think it is time now for the Society as a whole to realize that this procedure, both for diagnosis and for therapy, has a very well established past and a very active present.

Dr. Rawson (*closing*): I am interested in Dr. Corrigan's comments on the differences of the East Coast and the Midwest in the collection of iodine. We have had exactly the opposite impression in doing our studies and comparing with those of Dr. Raymond Keating at the Mayo Clinic, whose averages of excretion by normal human and antitoxic patients have been almost exactly the same as ours. The average for normals is about 65 or 66 per cent, and for thyrotoxic patients 19 or 20 per cent. The figures for myxedema are equally close.

I think it is important to point out that, in considering tracer studies with carrier-free iodine, oftentimes there may be a multiple layer of iodine left on the vessel and there may be a discrepancy in that.

Another thing I would like to point out, which I know will be of interest to you as radiologists, is that in patients who have recently had a gallbladder dye the excretion is less. We have demonstrated an excretion of 12 per cent before giving the dye and an excretion of 8 per cent after giving it.

There are side effects of large doses of radioactive iodine which we must consider and must consider very carefully. Mr. Marinelli pointed out the possibility of thyrotoxicosis from breakdown of the tissue. We have several patients in whom we have observed an increase in blood iodine within ten days after giving an increased dose of radioactive iodine. There have been changes in the blood picture following large doses in an attempt to control certain thyroid tumors.

A most interesting case studied jointly at

Memorial Hospital was one of lymphatic leukemia, with an overactive thyroid. The patient was given a destroying dose of radioactive iodine and had a fall in the white count to 15,000 in ten days. It is gradually rising now at the rate of about 1,000 a week.

Dr. Frantz (*closing*): I would like to thank Dr. Corrigan for his very kindly comment but I think an analytical mind might have appreciated the fact that thirty lantern slides cannot be shown adequately in twenty minutes.

I want belatedly to thank the Society for allowing me to speak before it. I noticed that another speaker from the Presbyterian Hospital also plunged right into the meat of the matter, whereas speakers from Massachusetts General Hospital had some manners, as did also Mr. Marinelli from Memorial Hospital in New York.

May I comment once more on thyroidectomy by surgery rather than by a sterilizing dose of radioactive iodine. I think that there is a theoretical argument for the enhancement or the aggrandizement of the function of the metastases when the gland is gone. In other words, the supply of hormone is demanded by the body and in the absence of the thyroid itself there may be a higher uptake in the metastatic foci, so that, if the gland is removed quickly, before any other therapy has reached the metastases, the possibility that they will swallow more of their own poison in the form of iodine is a good one.

There is one other theoretical consideration which has bothered me very much, particularly after our first patient's metastatic deposits varied so widely in their histologic grade of malignancy; that is the possibility that by administering these small doses incompetent to destroy the metastases we may be doing something to the biological nature of the cells, which may mean that they become less differentiated, perhaps, and have a higher invasive quality.

In closing, I would also like to say that, although nuclear fission may threaten to divide the world, it has consolidated, at least in our institution, departments not always wholly friendly, such as medicine and surgery, I being a humble member of the latter, and this consolidation is largely due to the Department of Radiological Research. Dr. Failla and Dr. Quimby have happily united old rivals.

Mr. Marinelli (*closing*): May I add just a word about units? The way I have standardized the administered dose of I^{131} at Memorial is by its gamma ray emission in roentgens. The constant is 2.6 roentgens per mc. hour at 1 cm. distance. I have checked the measurement with Dr. Peacock directly and checked with the Bureau of Standards lately, and we agree within 10 per cent, which I think is sufficient for the time being. I think most of the difficulty in interchecking is of a chemical nature. As Dr. Rawson has indicated, this point should be watched carefully, and each laboratory ought to have an independent means of making sure that its millicurie, whatever it is, is the same all the time. I think the use of an ionization chamber is much more advisable than that of a Geiger counter, if permanency of calibration is to be attained.

Dr. Chapman (*closing*): They say every program has its keynoter, and I think Dr. Corrigan sounded the keynote in this program when he spoke of teamwork. I want to say that the work we are doing is possible only because of teamwork. That teamwork was carried on very closely with the Massachusetts Institute of Technology, where several men were involved, and in the past year with Dr. Bengt Skanse of Sweden, who is here on a Rockefeller fellowship. The physicians and the physicists have to work in close co-operation.

Where radiation therapy for hyperthyroidism fits in will not be decided for perhaps ten or twenty years. We have to follow these patients. We are in an era of discovery. I am sure new discoveries will be presented at your meeting next year, and I look forward to the time—1960 perhaps—when a definite statement can be made as to the place of this form of treatment in the practice of medicine.

Dr. Werner (*closing*): May I amplify the words of Dr. Rawson about the effect of iodine on the tracer dose. No doubt gallbladder dye which contains iodine is an effective agent in blocking uptake. It is also blocked by previous administration of iodine in any form, so that a false reading of toxic goiter or of non-toxicity may be made depending upon the preceding use of iodine. Previous iodine lack may result in an unusual increase in the uptake of iodine, so that an error from this source may be possible, as well as the error from iodine excess. If a brief history is taken, however, the accuracy of the tracer method seems excellent, and although we have had a few discrepancies, they have not been many. In using these large doses of radioactive iodine, it must not be forgotten that this material is localized elsewhere in the body and is excreted by the kidneys. It also should be borne in mind that kidney function should be considered in the use of large doses of radioactive iodine.

EDITORIAL

The Memorial Fund

In the last few years the critical need of organized medicine for some financial background has become increasingly apparent. Some have contended that the annual dues should be higher in order to support our medical societies. They can cite comparable organizations and even organizations of medical offshoots as examples. Medical organizations could and should do more for their members. They should be able to provide more material for their scientific meetings, their clinical sessions, and their post-graduate endeavors. Medical organizations should be able to endow worth-while research and to aid fellowships, such as that in the Registry of Radiological Pathology to which our Society is giving its support.

These activities can be accomplished only by the co-ordinated efforts of the members and friends of the Radiological Society of North America. We have a Memorial Fund which was started by Dr. Robert H. Lafferty of Charlotte, North Carolina, in 1927. This Fund was created by the membership of the Society. It is administered by the Board of Trustees of the Fund, which is composed of five men: the President and the Secretary-Treasurer of the Radiological Society of North America and three members, who shall be past Presidents of the Society and serve for six years.

This Memorial Fund has remained static for several years. There are members donating to other foundations and organizations who probably do not know that we have such a Fund. I am sure that donations to this Fund are deductable from one's income tax, since the Radiological Society of North America is classified as a scientific organization.

Radiology has advanced by the consistent efforts of those practising this specialty. The proof of such a statement is exemplified in their activities in all organizations in which they hold membership. It is also exemplified in the fight against socialized medicine. We should build a Fund that will aid the members of the Radiological Society of North America to achieve its aims. The Fund must attain a size that will make the responsibilities of the Society more flexible and accomplish its purposes without increasing the dues. Endowments should be left without restrictions, as these tend to make any fund stagnant. We cannot foresee changing conditions.

I believe that the By-Laws should be changed to read that all income from the Fund "shall be used for charitable or educational purposes and the necessary expense incident thereto." This places on the Fund a general limitation within the highest ideals of the medical profession. The term "educational" is legally broad enough to include, together with the term "charitable," every altruistic endeavor of organized medicine. By placing these positive limitations upon the Fund, it falls within the legal status of those funds exempt from major income, inheritance, and gift taxes.

JOHN S. BOUSLOG, M.D.
For the Board of Directors,
Radiological Society of
North America

We Point With Pride

It seems fitting that in this Anniversary number some reference be made to the men who are so largely responsible for the comprehensive Abstract Section appearing monthly in RADIOLOGY. The publication of abstracts of the current literature of interest to radiologists has long been a feature of our journal. With the multiplication of medical publications and the increasing application of radiology to the problems of modern medicine, a service of this type has assumed greater and greater significance. It has at the same time involved more and more work. RADIOLOGY owes a real debt to the large staff of abstractors, representative of institutions throughout the country, who voluntarily contribute their services to bring to its readers a comprehensive review of the world's radiological literature.

We point with pride to the following radiologists who have contributed to the Abstract Section of Radiology during the past year:

William R. Allen, M.D.
Louis Bernstein, M.D.
Andrew K. Butler, M.D.
Horace G. Butler, M.D.
R. W. Byrn, M.D.
James T. Case, M.D.
C. P. Chrest, M.D.
Elizabeth A. Clark, M.D.
Max Climan, M.D.*
Charles B. Cobern, M.D.
John A. Cocke, M.D.
Benjamin Copleman, M.D.
Joseph T. Danzer, M.D.
John DeCarlo, M.D.
Percy J. Delano, M.D.
M. Wendell Dietz, M.D.
Alfred H. Dobrak, M.D.
Philip W. Dorsey, M.D.
Zac F. Endress, M.D.
Paul W. Eyler, M.D.
Jorge de la Flor, M.D.
John H. Freed, M.D.
Joseph Furnari, M.D.
Cesare Gianturco, M.D.
Frederick R. Gilmore, M.D.
Ellwood W. Godfrey, M.D.
Dr. Leonardo Guzman
Joseph Hanelin, M.D.
Alton S. Hansen, M.D.
Francis F. Hart, M.D.
Sydney J. Hawley, M.D.
John R. Hodgson, M.D.
John F. Holt, M.D.
John W. Hope, M.D.
Morris Ivker, M.D.
Lewis G. Jacobs, M.D.
Bernard S. Kalayjian, M.D.
James C. Katterjohn, M.D.
Ernest S. Kerekes, M.D.
D. A. Koch, M.D.
John O. Lafferty, M.D.
Edward E. Levine, M.D.
Eugene F. Lutterbeck, M.D.
John B. McAneny, M.D.
Stanley H. Macht, M.D.
R. S. MacIntyre, M.D.
David S. Malen, M.D.
Bert H. Malone, M.D.
Willis Manges, M.D.
Alfred O. Miller, M.D.
Glenn F. Miller, M.D.
Marlyn W. Miller, M.D.
D. B. Nagle, M.D.
P. Nemfakos, M.D.
Paul R. Noble, M.D.
Hugh A. O'Neill, M.D.
Stuart A. Patterson, M.D.
Lester W. Paul, M.D.
Robert C. Pendergrass, M.D.
Harold O. Peterson, M.D.
Everett L. Pirkey, M.D.
L. A. Poznak, M.D.
Arthur W. Pryde, M.D.
Edsel S. Reed, M.D.
Richard C. Ripple, M.D.
Vern W. Ritter, M.D.
Sava M. Roberts, M.D.
Paul W. Roman, M.D.
Maurice D. Sachs, M.D.
Stephen N. Tager, M.D.
Henry K. Taylor, M.D.
Sydney F. Thomas, M.D.
Joseph P. Tomsula, M.D.
Roderick L. Tondreau, M.D.
G. K. Vollmar, M.D.
Clarence E. Weaver, M.D.
M. D. Wertenberger, M.D.
John E. Whiteleather, M.D.
Daniel Wilner, M.D.
E. M. Wright, M.D.
H. H. Wright, M.D.

* Deceased.

RADIOLOGICAL SOCIETY OF NORTH AMERICA

THIRTY-FOURTH ANNUAL MEETING, SAN FRANCISCO
DEC. 5–DEC. 10, 1948
PRELIMINARY PROGRAM

Monday, December 6

GENERAL SESSION: 10:15 A.M.

CALL TO ORDER

L. H. GARLAND, M.D., President
San Francisco, Calif.

ADDRESS OF WELCOME

R. S. KNEESHAW, M.D.
President-Elect of California Medical Association

1. **PRESIDENTIAL ADDRESS**

L. H. GARLAND, M.D.

SYMPOSIUM ON SKELETAL CALCIUM DISTURBANCES

2. Skeletal Changes Associated with Certain Endocrine Disturbances. FULLER ALBRIGHT, M.D., Boston, Mass.
3. The Pathology of the Skeleton as Seen in the Bones of the Hand. J. F. BRAILSFORD, M.D., Birmingham, England.

JOINT SESSION: 2:00 P.M.

SYMPOSIUM ON RADIOACTIVE ISOTOPES

W. E. Chamberlain, M.D., Philadelphia, Penna., Presiding

4. "Wet Clinic" on Radioactive Isotopes. W. E. CHAMBERLAIN, M.D., Philadelphia, *Presiding;* R. R. NEWELL, M.D., San Francisco; EDITH H. QUIMBY, SC.D., New York; EARL R. MILLER, M.D., San Francisco; R. H. CHAMBERLAIN, M.D., Philadelphia; GEORGE C. HENNY, M.D., Philadelphia.
5. Recent Developments in Radioisotope Distribution. P. C. AEBERSOLD, PH.D., Oak Ridge, Tenn.
6. Instrumentation for Therapeutic Radioisotope Application. S. L. WARREN, Los Angeles, Calif.

MEMBERSHIP DINNER: 7:00 P.M.

Tuesday, December 7

JOINT SESSION: 10:15 A.M.

SYMPOSIUM ON CHEMICAL EFFECTS OF IRRADIATION

Robert S. Stone, San Francisco, Presiding

7. Relationships Between Chemical and Biological Effects of Ionizing Radiations. R. E. ZIRKLE, PH.D., Chicago, Ill.
8. Chemical Effects of Ionizing Radiation. JAMES FRANCK, PH.D., Chicago, Ill.
9. Comparative Studies on the Biological Effects Produced by Radiation and Chemical Agents. LEON O. JACOBSON, M.D., Chicago, Ill.

DIAGNOSTIC SESSION: 2:00 P.M.

SYMPOSIUM ON PEPTIC ULCER

Joseph C. Bell, M.D., Louisville, Ky., Presiding

10. Peptic Ulcer—The Importance of Films in Diagnosis. FREDERIC E. TEMPLETON, M.D., Seattle, Wash.
11. The Place of Fluoroscopy in the X-Ray Diagnosis of Peptic Ulcer. MILO T. HARRIS, M.D., Spokane, Wash.
12. Physical Problems of Fluoroscopy and Spot Film Radiography. RUSSELL H. MORGAN, M.D., Baltimore, Md.
13. Value of Gastroscopy in Peptic Ulcer. MORRIS E. DAILEY, M.D., San Francisco, Calif.
14. Peptic Ulcer: Modern Criteria for Diagnosis and Attempted Diagnosis of Healing. DWIGHT L. WILBUR, M.D., AND MALCOLM S. WATTS, M.D., San Francisco, Calif.
15. Downward Displacement of the Gastric Cardia. FRED J. HODGES, M.D., Ann Arbor, Mich.

THERAPY SESSION: 2:00 P.M.

Milton Friedman, M.D., New York, Presiding

16. The Nature of Radiation Injury as Seen by the Geneticist. H. J. MULLER, PH.D., Bloomington, Ind.
17. Further Studies on the Relation between Radiation Effects, Cell Viability, and Induced Resistance to Malignant Growth. ANNA GOLDFEDER, D.SC., New York, N. Y.
18. Tentative Dose Units for Mixed Radiations. H. M. PARKER, PH.D., Richland, Wash.
19. Dosage Distribution and Dosage in the Treatment of Carcinoma of the Uterine Cervix. W. J. MEREDITH, M.SC., Manchester, England.
20. The Clinical Usefulness and Limitations of Supervoltage Roentgen Therapy. SIMEON T. CANTRIL, M.D., AND FRANZ BUSCHKE, M.D., Seattle, Wash.
21. Roentgen Therapy for Pituitary Adenoma: Correlation of Tumor Dose with End Results. ARNOLD L. BACHMAN, M.D., AND WILLIAM HARRIS, M.D., New York, N. Y.

THE CARMAN LECTURE: 8:00 P. M.

Merrill C. Sosman, M.D.

Wednesday, December 8

DIAGNOSTIC SESSION: 10:15 A.M.

SYMPOSIUM ON PULMONARY DISORDERS

E. P. McNamee, M.D., Cleveland, Ohio, Presiding

22. Spontaneous Pneumothorax: A Study of 105 Cases. R. GOLDEN, M.D., AND L. A. ROTTENBERG, M.D., New York, N. Y.
23. Radiological Manifestations of Bronchial Dynamism. S. DI RIENZO, M.D., Cordoba, Argentina.
24. A Correlation of the Roentgenologic and Pathologic Findings in Cholesterol Pneumonitis. LAURENCE L. ROBBINS, M.D., Boston, Mass.
25. Active Bronchopulmonary Lithiasis. EUGENE FREEDMAN, M.D., AND J. H. BILLINGS, M.D., Los Angeles, Calif.
26. "Egg-Shell" Calcifications in Silicosis. C. E. GRAYSON, M.D., AND HELEN BLUMENFELD, M.D., Sacramento, Calif.

THERAPY SESSION: 10:15 A.M.

27. Radium Therapy in Carcinoma of the Female Urethra. R. E. FRICKE, M.D., AND J. T. McMILLAN, M.D., Rochester, Minn.
28. A New Radium Technic for Carcinoma of the Bladder. M. FRIEDMAN, M.D., AND L. LEWIS, M.D., New York, N. Y.
29. Carcinoma of the Thyroid Gland: An Analysis of All Cases Admitted to the Brooklyn Cancer Institute. W. E. HOWES, M.D., Brooklyn, N. Y.
30. Graves' Disease: Twenty-Five Year Follow-Up of Roentgen Therapy. J. M. READ, M.D., San Francisco, Calif.
31. Roentgen Therapy of Carcinomas of Skin of the Eyelid. J. A. DEL REGATO, M.D., Columbia, Mo.

DIAGNOSTIC SESSION: 2:00 P.M.

SYMPOSIUM ON CONGENITAL AND OTHER CARDIOVASCULAR DISORDERS

Leo G. Rigler, M.D., Minneapolis, Minn., Presiding

32. Clinical Diagnosis of Congenital Heart Disease by Conventional Methods. MORSE J. SHAPIRO, M.D., Minneapolis, Minn.
33. The Conventional Roentgen Examination in Operable Congenital Heart Disease. HERBERT STAUFFER, M.D., Minneapolis, Minn.
34. Conventional Roentgenographic Technics in Diagnosis of Cardiovascular Anomalies. HUGH WILSON, M.D., New Haven, Conn.
35. The Diagnosis of Congenital Heart Disease by Improved Methods for the Automatization of the Radiographic Technics. W. G. SCOTT, M.D., St. Louis, Mo.
36. Superior Retrograde Aortography in the Diagnosis of Coarctation. RAÚL PEREIRAS, M.D., Habana, Cuba.
37. Some Clinical Applications of Electrokymography. M. L. SUSSMAN, M.D., S. DACK, M.D., AND D. H. PALEY, M.D., New York, N. Y.

37A. The Roentgen Findings in Acute Thrombosis. DR. J. FRIMANN-DAHL, Oslo, Norway.

THERAPY SESSION: 2:00 P.M.

VISIT TO CYCLOTRON

Thursday, December 9

DIAGNOSTIC SESSION: 10:15 A.M.

SYMPOSIUM ON INTRACRANIAL LESIONS

B. R. Young, M.D., Philadelphia, Penna., Presiding

38. The Roentgen Demonstration of Displaced Intracranial Physiologic Calcification and Its Significance in the Diagnosis of Brain Tumors and Other Space-Occupying Disease. B. R. YOUNG, M.D., Philadelphia, Penna.
39. The Roentgen Manifestations of Cerebellopontine Angle Tumors. P. J. HODES, M.D., E. P. PENDERGRASS, M.D., AND B. R. YOUNG, M.D., Philadelphia, Penna.
40. Roentgenologic Observations Concerning Erosion of the Sella Turcica. J. D. CAMP, M.D., Rochester, Minn.
41. Meningiomas of the Sphenoidal Ridge. E. P. PENDERGRASS, M.D., C. R. PERRYMAN, M.D., AND J. W. HOPE, M.D., Philadelphia, Penna.
42. Spinal Cord Tumors. JOHN R. HANNAN, M.D., C. R. HUGHES, M.D., AND BERT E. MULVEY, M.D., Cleveland, Ohio.

THERAPY SESSION: 10:15 A.M.

Ira Lockwood, M.D., Kansas City, Mo., Presiding

43. Plea for the Early Recognition of Malignant Melanoma. R. R. BRAUND, M.D., Memphis, Tenn.
44. Alpha Rays in the Treatment of Radiation Injuries. E. M. UHLMANN, M.D., Chicago, Ill.

SYMPOSIUM ON BIOPSY AND CYTOPSY METHODS

45. The Value and Limitations of Aspiration Biopsy for Lung Lesions. G. P. ROSEMOND, M.D., W. E. BURNETT, M.D., AND J. H. HALL, M.D., Philadelphia, Penna.
46. Evaluation of Needle Aspiration Technic in Lesions of the Breast. J. W. BUDD, M.D., Los Angeles, Calif.
47. Bronchogenic Carcinoma: Diagnosis by Means of Cytological Examination of Sputum and Bronchial Secretions. S. M. FARBER, M.D., M. A. BENIOFF, M.D., AND A. K. MCGRATH, JR., M.D., San Francisco Calif.

DIAGNOSTIC SESSION: 2:00 P.M.

SYMPOSIUM ON BONE AND JOINT DISORDERS

Howard P. Doub, M.D., Detroit, Mich., Presiding

48. Studies on the Scope of Pneumarthrography of the Knee as a Diagnostic Aid. M. D. SACHS, M.D., Cleveland, Ohio.
49. Traumatic and Degenerative Lesions of the Articular Cartilage of the Knee. R. SOTO-HALL, M.D., AND K. O. HALDEMAN, M.D., San Francisco, Calif.
50. Orthographic Pelvimetry. P. C. HODGES, M.D., AND R. L. NICHOLS, M.D., Chicago, Ill.
51. The Osseous Lesions of Sarcoidosis. J. F. HOLT, M.D., W. I. OWENS, M.D., AND A. C. CURTIS, M.D., Ann Arbor, Mich.
52. Bone-Calcium Evaluation from the Roentgenogram. GEORGE C. HENNY, M.D., Philadelphia, Penna.
53. High Kilovoltage Radiography. E. D. TROUT, PH.D., D. E. GRAVES, AND D. B. SLAUSON, Milwaukee, Wis.

THERAPY SESSION: 2:00 P.M.

PANEL DISCUSSION ON PERMISSIBLE TOTAL BODY IRRADIATION (ACUTE-POST ATOMIC)

E. P. Pendergrass, M.D., Philadelphia, Penna., Chairman

54. Permissible Full Body Irradiation in Emergency Zones. E. P. PENDERGRASS, M.D., Philadelphia, Penna.
55. Summary of Available Physical Data on Atomic Radiations. EDITH H. QUIMBY, Sc.D., New York, N. Y.
56. Summary of Available Experimental Data on Acute and Chronic Tolerance Doses. EGON LORENZ, PH.D., Bethesda, Md.
57. Clinical Effects of Acute Atomic Total Body Radiation. R. S. STONE, M.D., San Francisco, Calif.
58. The Problem of Dosage Measurements for Radiations Produced by the Betatron. LAURISTON S. TAYLOR, PH.D., AND HAROLD O. WYCKOFF, PH.D., Bethesda, Md.
59. The Depth Dose of Electrons from the Betatron. L. S. SKAGGS, PH.D.

Friday, December 10

DIAGNOSTIC SESSION: 10:15 A.M.

John S. Bouslog, M.D., Denver, Col., Presiding

60. Fast Roentgen Visceral Survey. C. GIANTURCO, M.D., Urbana, Ill.
61. The Roentgenologic Diagnosis of Disease of the Ileocecal Coil. J. R. HODGSON, M.D., AND H. M. WEBER, M.D., Rochester, Minn.
62. Massive Calcification in Infarcted Myocardium. H. P. BREAN, M.D., Palo Alto, Calif., J. H. MARKS, M.D., Boston, Mass., M. C. SOSMAN, M.D., Boston, Mass., AND M. J. SCHLESINGER, M.D., Boston, Mass.
63. Acute Pulmonary Edema Resulting from Intravenous Saline. J. E. WHITELEATHER, M.D., AND J. E. GARDNER, M.D., Memphis, Tenn.
64. Acute Primary Pulmonary Blastomycosis. CHESTER BONOFF, M.D., Los Angeles, Calif.

THERAPY SESSION: 10:15 A.M.

SYMPOSIUM ON CHEMOTHERAPY, STEROIDS AND MISCELLANEOUS TOPICS

Kenneth S. Davis, M.D., Los Angeles, Calif., Presiding

65. Experimental Chemotherapy of Neoplastic Diseases. M. B. SHIMKIN, M.D., AND H. R. BIERMAN, M.D., San Francisco, Calif.
66. The Action of Steroid Hormones in Mammary Cancer. W. VAN WINKLE, JR., M.D., Chicago, Ill.
67. Roentgen Therapy and the Relief of Pain. F. W. O'BRIEN, M.D., Boston, Mass.
68. The Responsibility of the Radiologist in the Treatment of Advanced Malignant Disease. J. R. MAXFIELD, JR., M.D., AND J. G. S. MAXFIELD, M.D., Dallas, Tex.
69. Clinical Evaluation of the Radiation Effects in Carcinoma of the Cervix with the Expanding Type Radium Applicator. EDWIN C. ERNST, M.D., St. Louis, Mo.

JOINT SESSION: 2:00 P.M.

SYMPOSIUM ON PEDIATRIC PROBLEMS

Charles H. Heacock, M.D., Memphis, Tenn., Presiding

70. Congenital Obstruction of the Alimentary Tract in Infants and Children. JOHN CAFFEY, M.D., AND F. N. SILVERMAN, M.D., New York, N. Y.
71. The Reliability of the Roentgen Diagnosis of Hypertrophic Pyloric Stenosis. H. W. HEFKE, M.D., Milwaukee, Wis.
72. Aspiration Pneumonia in Children. CHARLES H. HEACOCK, M.D., Memphis, Tenn.
73. Radiology in Neurosurgical Conditions of Childhood. NICHOLAS GOTTEN, M.D., AND C. D. HAWKES, M.D., Memphis, Tenn.
74. Roentgenological Findings in Sickle Cell Anemia. D. S. CARROLL, M.D., AND J. W. EVANS, M.D., Memphis, Tenn.
75. Some Clinical Applications of Cineradiography. GEORGE H. RAMSEY, M.D., JAMES S. WATSON, JR., M.D., SYDNEY WEINBERG, FRANK DREISINGER, R. T., AND JOHN J. THOMPSON, M.D., Rochester, N. Y.

ANNOUNCEMENTS AND BOOK REVIEWS

SAN FRANCISCO MEETING

TENTATIVE PROGRAM FOR LADIES' ENTERTAINMENT

Sunday, Dec. 5

Registration at Ladies' Registration Desk, Fairmont Hotel lobby	2:30 P.M.

Monday, Dec. 6

Registration	10:00 A.M.
*City tour with luncheon at one of the country clubs	11:00 A.M.
*Conducted tour through Chinatown	8:00 P.M.

Tuesday, Dec. 7

Registration	10:00 A.M.
Private shopping service. Please make arrangements at Ladies' Registration Desk	
*Tea and fashion show	4:00 P.M.
Carman Lecture, Fairmont Hotel	8:00 P.M.

Wednesday, Dec. 8

Registration	10:00 A.M.
*Bus trip to University of California and demonstration of Cyclotron	2:30 P.M.

Thursday, Dec. 9

Registration	10:00 A.M.
Visit to Gump's jade collection	11:00 A.M.
Banquet (formal)	7:30 P.M.

* Tickets for all events may be purchased separately and are to be procured at Ladies' Registration Desk.

MRS. ROBERT S. STONE
MRS. B. V. LOW-BEER
Co-Chairmen, Ladies' Entertainment Committee

FLORIDA RADIOLOGICAL SOCIETY

The recently elected officers of the Florida Radiological Society are as follows: President, Dr. J. F. Pittman, Lake City; Vice-President, Dr. J. A. Beals, Jacksonville; Secretary-Treasurer, Dr. F. K. Hurt, Jacksonville.

ROCKY MOUNTAIN RADIOLOGICAL SOCIETY

The annual meeting of the Rocky Mountain Radiological Society was held in Salt Lake City, on August 12, 13, and 14. The meeting was a success both from the scientific and social aspects. The following men were guest speakers: Dr. L. Henry Garland, Dr. John Caffey, Dr. Ross Golden, Dr. Juan A. del Regato, Dr. John D. Camp, and Dr. Wendell G. Scott.

The officers elected for the coming year are: President, Dr. Howard B. Hunt, Omaha, Nebr.; President Elect, Dr. Kenneth D. A. Allen, Denver, Colo.; First Vice-President, Dr. M. Lowry Allen, Salt Lake City, Utah; Second Vice-President, Dr. Thomas Bond, Fort Worth, Texas; Secretary-Treasurer, Dr. Maurice D. Frazer, Lincoln, Nebr. Dr. Ira H. Lockwood, Dr. Paul Weeks, and Dr. Edward J. Meister were elected to the Program Committee and Dr. James P. Kerby, Dr. A. M. Popma, and Dr. W. Walter Wasson to the Executive Committee.

SOCIEDAD DE RADIOLOGÍA, CANCEROLOGÍA Y FISICA MEDICA DEL URUGUAY

Announcement has recently been received of the reorganization of the Sociedad de Radiologfa, Cancerologfa y Fisica Medica of Uruguay. The officers of the Society are: President, Dr. Felix Leborgne; Vice-President, Dr. Alfonso Frangella; Secretary-General, Dr. Hector Bazzano; Secretary, Dr. Arias Bellini; Treasurer, Dr. Luis Vazquez Piera; Chancellors, Dr. Mario Cassinoni and Dr. Agustin Gorlero Armas.

THIRD INTER-AMERICAN CONGRESS OF RADIOLOGY

A preliminary notice of the Third Inter-American Congress of Radiology appeared in the January 1948 issue of RADIOLOGY. The date for the Congress has now been set, Nov. 11–17, 1949. Dr. Felix J. Daza is Chairman of the Executive Committee and Dr. Alberto H. Ricci, General Treasurer. The General Secretaries are Dr. Cesar Velasco for the United States and Canada and Dr. Santiago H. Calderon for Latin America. The official address is Comite Ejecutivo del III Congreso Inter-Americano de Radiologia, Casilla 693, Santiago de Chile. There has been appointed a co-ordinator in each country, Dr. James T. Case, of Chicago, representing the United States.

The official subjects, as previously announced, are (1) Radiological Exploration of the Cardiovascular System with Opaque Material; (2) Diagnosis and Simple Radiological Exploration of the Skull; (3) Radiation Treatment of Cancer of the Tongue; (4) Radiation Treatment of Cancer of the Cervix.

Letter to The Editor

TO THE EDITOR OF RADIOLOGY

DEAR DR. DOUB:

You will recall that in May of this year you published an Abstract, which I had prepared, of a paper by Albot and Marquis on the "Study of the Mucosal Relief in Early Cancer of the Stomach

with the Aid of Pharmaco-radiography." I believe that this method is of real practical importance, and I am happy to be able to give you more details regarding it. I am in a position to do this, since Prof. Réné Guttmann of Paris has been here and has delivered some lectures and given some convincing demonstrations of the procedure.

Twenty minutes before administration of barium to the fasting patient, Dr. Guttmann injects 1 cg. of morphine subcutaneously. Some workers make the same injection intravenously but he prefers the subcutaneous route. Others inject insulin (20 international units) instead of morphine, ten minutes before giving barium. Dr. Guttmann emphasized the necessity of compression during fluoroscopy and at the moment of taking the film, since, after administration of morphine, the excitation of the muscles of the stomach is very active and the compression is useful to show more relevant details of the lesion.

The procedure is indicated in patients with atonic stomach and in cases where the image of the lesser curvature is not definite and clear cut. The injection produces great excitability followed by contraction, with the result that suspected infiltration or ulceration becomes clearly visible, permitting an accurate conclusion. Dr. Guttmann emphasized that the first suspicious sign of an actual lesion, especially in cancer of the antrum, is a widening of the acute angle formed by the lesser curvature with the pylorus. He also mentioned that the morphine provokes great distention of the second portion of the duodenum.

For demonstration of small-intestinal lesions, 1.5 c.c. of a 1:2000 solution of prostigmine solution is given intravenously, twenty or thirty minutes after barium administration with excellent results.

I hope that it will be possible for you to publish this information as a supplement to the earlier abstract.

Most sincerely yours
DR. LEONARDO GUZMAN
Santiago de Chile

Books Received

Books received are acknowledged under this heading, and such notice may be regarded as recognition of the courtesy of the sender. Reviews will be published in the interest of our readers and as space permits.

STANDARD RADIOGRAPHIC POSITIONS. By NANCY DAVIES, M.S.R., C.T., Senior Radiographer, Malvern General Hospital, Malvern; Formerly Sgt./Radiographer-in-charge, Queen Alexandra Military Hospital, Millbank, London (attached No. 18 Coy. R.A.M.C.), and Radiographer-in-charge, Royal Surrey County Hospital, Guildford, Royal Gwent Hospital, Newport, Caernarvonshire and Anglesey Infirmary, Bangor, Royal Infirmary, Worcester, and Radiographer, Royal Infirmary, Derby, and URSEL ISENBURG, M.S.R., Radiographer, Royal Free Hospital, London, Formerly Radiographer, Willesden General Hospital, London, London Homeopathic Hospital, Research Worker, Institut Municipal d'Electro-Radiologie (Prof. Zimmern), Paris, and Radiographer, Rudolf Virchow Hospital (Dr. G. Bucky), Berlin. A volume of 223 pages, with 384 illustrations. Published by The University Press, Aberdeen; The Williams & Wilkins Co., Baltimore, 2d ed., 1948. Price $6.00.

THE TREATMENT OF MALIGNANT DISEASE BY RADIUM AND X-RAYS, BEING A PRACTICE OF RADIOTHERAPY. By RALSTON PATERSON, M.C., M.D., F.R.C.S.E., D.M.R.E., F.F.R., Christie Hospital and Holt Radium Institute, Manchester. A volume of 622 pages, with numerous figures, tables, and charts. Published by Butler and Tanner, Ltd., Frome and London; The Williams & Wilkins Co., Baltimore, 1948. Price $11.00.

Book Reviews

MODERN TRENDS IN DIAGNOSTIC RADIOLOGY. Edited by J. W. MCLAREN, M.A., M.R.C.S., L.R.C.P., D.M.R.E., Director, X-Ray (Diagnostic) Department, St. Thomas's Hospital, London; Examiner in Radiology, University of London. A volume of 464 pages, with 381 illustrations. Published by Paul B. Hoeber, Inc., New York and London, 1948. Price $12.00.

In this volume an attempt has been made to record some of the advances that have been made in diagnostic roentgenology during the past decade. Because of the very nature of the subject, however, more than this period is covered.

Thirty-one chapters are largely the work of writers from the British Isles, but there is one chapter by Baclesse of Paris, several of the Scandinavian countries are represented, and Newell of San Francisco has contributed two chapters. The subjects are so diverse that they cannot be detailed in this review but many diagnostic problems are covered, both specific—such as sarcoidosis and renal tuberculosis—and general—such as modern trends in gastroenterology and abnormalities of the spine.

The treatment of the subject matter seems to have been left largely to the individual authors and therefore varies widely. Some cover their subjects rather briefly, without documentation, while others go into much fuller detail, with reviews of the pertinent literature. In general, however, there is a good deal of informative material on unusual subjects not as a rule found in a textbook on diagnosis.

The book is printed on good paper and the general format is attractive. Most of the cuts are of excellent quality. The text is recommended not as

attempting to cover the entire subject of diagnostic roentgenology but as containing a large fund of valuable information on many diverse subjects.

THE RADIOLOGY OF BONES AND JOINTS. By JAMES F. BRAILSFORD, M.D., PH.D., F.R.C.P., F.I.C.S., Hunterian Professor, Royal College of Surgeons, England, 1934–5, 1943–4; Founder and First President of The British Association of Radiologists (now the Faculty of Radiologists); Director of Radiological Studies in Living Anatomy, the University of Birmingham; Honorary Radiologist to the Queen Elizabeth Hospital, Birmingham, the Royal Cripples' Hospital, and the Warwickshire Orthopaedic Hospital; Radiologist to St. Chad's Hospital, the City of Birmingham Infant Welfare Centres and the Military Hospital, Hollymoor, Birmingham; Consulting Radiologist to the City of Birmingham Hospitals, etc. Awarded the Robert Jones Gold Medal and Prize of the British Orthopaedic Association, 1927, the Roentgen Prize, 1936. Fourth Edition, 1948. A volume of 760 pages with 615 illustrations. Published by J. & A. Churchill Ltd., London, price, 63s, and by Williams and Wilkins, Baltimore, Md., price $15.00.

Brailsford's excellent and comprehensive textbook on "Radiology of the Bones and Joints" has long been established as one of the preferred reference works on the radiological study of skeletal pathology. The new Fourth Edition not only lives up to but surpasses the earlier editions. There has been a thorough revision of the text, with additions covering the world's literature which has accumulated since 1944, when the Third Edition appeared.

The general plan of presentation is retained. The first section, comprising 535 pages, covers the radiography of the skeleton from a regional standpoint, taking up in succession the lesions which occur in the various anatomical subdivisions. Part II, 185 pages, is devoted to consideration of certain bony abnormalities and diseases which have a more general distribution.

Two hundred illustrations of excellent quality have been added to an already generous number. Many new references are included, bringing the bibliography to 15 pages. An excellent index makes the recorded material readily available.

This volume will find a welcome place in the libraries of radiologists and students of skeletal pathology.

In Memoriam

MAX CLIMAN, M.D.

1892–1948

Dr. Max Climan died on Aug. 18 in the Mt. Sinai Hospital, Hartford, Conn., after a brief illness.

Dr. Climan was born in Hartford in 1892. He was graduated from Yale University in 1913 and

Max Climan, M.D.

from the College of Physicians and Surgeons, Columbia University, in 1914, and served his internship at Lebanon Hospital, New York. He was with Base Hospital 60 in France in World War I and was discharged with the rank of Captain.

For twenty-nine years Dr. Climan was engaged in the practice of radiology in his native city. He was on the staff of Mt. Sinai, McCook Memorial, and the Newington Veterans Hospitals. He was a member of the Connecticut and Hartford Medical Societies, of the A. M. A., the Radiological Society of North America, the New England Roentgen Ray Society, and the American College of Radiology. He was secretary of the Connecticut Radiological Society for many years and also served as its president.

Dr. Climan was an accomplished violinist and was a member of the orchestra of the Hartford School of Music and was at one time president of the West Hartford Civic Orchestra.

For a period of years Dr. Climan had been one of the volunteer abstract staff of RADIOLOGY. The faithful and efficient service which he rendered to the Journal, and through it to the Radiological Society of North America, will long be remembered.

It may be permitted here to quote briefly from a letter received from Dr. Climan's son, Marshall, as the most fitting tribute we could offer: "My father was not a man who sought acclaim or recognition.

He had a deep sense of duty to his profession, and I believe he carried it out to the fullest. He tried to be a good doctor and roentgenologist, and I think he was."

Beside his son, Dr. Climan is survived by his widow, Minerva Efros Climan.

EDWIN LOUIS RYPINS, M.D.

1903–1948

Dr. Edwin Louis Rypins died on July 4, 1948, at Brokaw Hospital, Normal, Ill., from injuries received in an automobile accident on July 1.

Dr. Rypins was born on Jan. 8, 1903. He received his degree in medicine from the University of Nebraska in 1927, following his medical course by a rotating internship at Scranton State Hospital, Penna., in 1927–28, and a residency at the Ridley Park Hospital, Penna., in 1928–29. He then engaged in general practice at Chester, Penna., in 1929–30. His postgraduate work in radiology was done in Iowa State Hospital, under Dr. H. Dabney Kerr.

Dr. Rypins became a member of the Radiological Society of North America in 1933, was certified by the American Board of Radiology in 1934, and became a member of the American Roentgen Ray Society in 1935. He was elected a Fellow of the American College of Radiology in 1943.

Except for the war years, Dr. Rypins was engaged in the practice of radiology in Bloomington, Ill., from 1935 to 1948. In September 1942 he enlisted in the Army of the United States with the rank of major, and was first assigned to medical units in Louisiana and Texas. He served as Chief of the X-Ray Department of the 69th General Hospital in the Ledo-Assam, China, Burma, and India theaters, after which he was with the 233rd and the 9th General Hospitals in Manila, as Chief of the X-Ray Department. He was promoted to the rank of Lt. Colonel in January and was discharged from service in October 1946. He was awarded the European Theater Ribbon, Asiatic-Pacific Medal with one Battle Star, the World War II Victory Medal, and the Occupation "Japan" Clasp.

Edwin Louis Rypins, M.D.

Dr. Rypins was a member of the Illinois State Medical Society, and was elected secretary of the Section on Radiology at the 1948 meeting. He was a member of the McLean County Medical Society, and on the staff of Brokaw Hospital, Normal, Ill. He was a member of the American Legion and the Army Reserve Corps.

The many friends and professional colleagues of Dr. Rypins will remember his outstanding honesty, loyalty, and generosity. He was a man of keen wit and fine scientific appreciation. Medicine in general and radiology in particular have lost a friend and a scholar. He is survived by his widow, Martha Cannon Rypins, whom he married in 1933.

HAROLD P. SHINALL, M.D.

RADIOLOGICAL SOCIETIES: SECRETARIES AND MEETING DATES

Editor's Note: Secretaries of state and local radiological societies are requested to co-operate in keeping this section up-to-date by notifying the editor promptly of changes in officers and meeting dates.

UNITED STATES

RADIOLOGICAL SOCIETY OF NORTH AMERICA. *Secretary-Treasurer*, Donald S. Childs, M.D., 713 E. Genesee St., Syracuse 2, N. Y.

AMERICAN RADIUM SOCIETY. *Secretary*, Hugh F. Hare, M.D., 605 Commonwealth Ave., Boston 15, Mass.

AMERICAN ROENTGEN RAY SOCIETY. *Secretary*, Harold Dabney Kerr, M.D., Iowa City, Iowa.

AMERICAN COLLEGE OF RADIOLOGY. *Secretary*, Mac F. Cahal, 20 N. Wacker Dr., Chicago 6, Ill.

SECTION ON RADIOLOGY, A. M. A. *Secretary*, U. V. Portmann, M.D., Cleveland Clinic, Cleveland 6, Ohio.

Alabama

ALABAMA RADIOLOGICAL SOCIETY. *Secretary-Treasurer*, W. D. Anderson, M.D., 2501 6th St., Tuscaloosa.

Arkansas

ARKANSAS RADIOLOGICAL SOCIETY. *Secretary*, Fred Hames, M.D., Pine Bluff. Meets every three months and at meeting of State Medical Society.

California

CALIFORNIA MEDICAL ASSOCIATION, SECTION ON RADIOLOGY. *Secretary*, Sydney F. Thomas, M.D., Palo Alto Clinic, Palo Alto.

LOS ANGELES RADIOLOGICAL SOCIETY. *Secretary*, Moris Horwitz, M.D., 2009 Wilshire Blvd., Los Angeles 5. Meets second Wednesday of each month at County Society Bldg.

NORTHERN CALIFORNIA RADIOLOGICAL CLUB. *Secretary*, Charles E. Grayson, M.D., Medico-Dental Bldg., Sacramento 14. Meets at dinner last Monday of September, November, January, March, and May.

PACIFIC ROENTGEN SOCIETY. *Secretary*, L. Henry Garland, M.D., 450 Sutter St., San Francisco 8. Meets annually with State Medical Association.

SAN DIEGO ROENTGEN SOCIETY. *Secretary*, R. F. Niehaus, M.D., 1831 Fourth Ave., San Diego. Meets first Wednesday of each month.

X-RAY STUDY CLUB OF SAN FRANCISCO. *Secretary*, Ivan J. Miller, M.D., 49 Fourth St. Meets monthly on the third Thursday at 7:45 P.M., January to June at Lane Hall, Stanford University Hospital, and July to December at Langley Porter Clinic, University of California Hospital.

Colorado

DENVER RADIOLOGICAL CLUB. *Secretary*, Mark S. Donovan, M.D., 306 Majestic Bldg., Denver 2. Meets third Friday of each month, at the Colorado School of Medicine and Hospitals.

Connecticut

CONNECTICUT STATE MEDICAL SOCIETY, SECTION ON RADIOLOGY. *Secretary*, Robert M. Lowman, M.D., Grace-New Haven Hospital, Grace Unit, New Haven. Meetings bimonthly, second Thursday.

District of Columbia

RADIOLOGICAL SECTION, DISTRICT OF COLUMBIA MEDICAL SOCIETY. *Secretary*, Alfred A. J. Den, M.D., 1801 K St., N. W., Washington 6. Meets third Thursday, January, March, May, and October, at 8:00 P.M., in Medical Society Auditorium.

Florida

FLORIDA RADIOLOGICAL SOCIETY. *Secretary-Treasurer*, F. K. Hurt, M.D., Riverside Hospital, Jacksonville. Meets in April and in November.

Georgia

GEORGIA RADIOLOGICAL SOCIETY. *Secretary-Treasurer*, Robert Drane, M.D., De Renne Apartments, Savannah. Meets in November and at the annual meeting of State Medical Association.

Illinois

CHICAGO ROENTGEN SOCIETY. *Secretary*, T. J. Wachowski, M.D., 310 Ellis Ave., Wheaton. Meets at the Palmer House, second Thursday of October, November, January, February, March, and April, at 8:00 P.M.

ILLINOIS RADIOLOGICAL SOCIETY. *Secretary-Treasurer*, William DeHollander, M.D., St. Johns' Hospital, Springfield. Meetings quarterly as announced.

ILLINOIS STATE MEDICAL SOCIETY, SECTION ON RADIOLOGY. *Secretary*, John H. Gilmore, M.D., 720 N. Michigan Ave., Chicago 11.

Indiana

INDIANA ROENTGEN SOCIETY. *Secretary-Treasurer*, William M. Lochr. M.D., 712 Hume-Mansur Bldg., Indianapolis 4. Annual meeting in May.

Iowa

IOWA X-RAY CLUB. *Secretary*, Arthur W. Erskine, M.D., 326 Higley Building, Cedar Rapids. Meets during annual session of State Medical Society.

Kansas

KANSAS RADIOLOGICAL SOCIETY. *Secretary-Treasurer*, Anthony F. Rossitto, M.D., Wichita Hospital, Wichita. Meets annually with State Medical Society.

Kentucky

KENTUCKY RADIOLOGICAL SOCIETY. *Secretary-Treasurer*, Sydney E. Johnson, M.D., 101 W. Chestnut St., Louisville.

LOUISVILLE RADIOLOGICAL SOCIETY, *Secretary-Treasurer*, Everett L. Pirkey, Louisville General Hospital, Louisville 2. Meets second Friday of each month at Louisville General Hospital.

Louisiana

LOUISIANA RADIOLOGICAL SOCIETY. *Secretary-Treasurer*, Johnson R. Anderson, M.D., No. Louisiana Sanitarium, Shreveport. Meets with State Medical Society.

ORLEANS PARISH RADIOLOGICAL SOCIETY. *Secretary*, Joseph V. Schlosser, M.D., Charity Hospital of Louisiana, New Orleans 13. Meets first Tuesday of each month.

SHREVEPORT RADIOLOGICAL CLUB. *Secretary*, Oscar O. Jones, M.D., 2622 Greenwood Road. Meets monthly September to May, third Wednesday.

Maryland

BALTIMORE CITY MEDICAL SOCIETY, RADIOLOGICAL SECTION. *Secretary*, J. Howard Franz, M.D., 1127 St. Paul St., Baltimore 2.

Michigan

DETROIT X-RAY AND RADIUM SOCIETY. *Secretary-Treasurer*, E. R. Witwer, M.D., Harper Hospital, Detroit 1. Meetings first Thursday, October to May, at Wayne County Medical Society club rooms.

MICHIGAN ASSOCIATION OF ROENTGENOLOGISTS. *Secretary-Treasurer*, R. B. MacDuff, M.D., 220 Genesee Bank Building, Flint 3.

Minnesota

MINNESOTA RADIOLOGICAL SOCIETY. *Secretary*, C. N. Borman, M.D., 802 Medical Arts Bldg., Minneapolis 2. Meets in Spring and Fall.

Missouri

RADIOLOGICAL SOCIETY OF GREATER KANSAS CITY. *Secretary*, Wm. M. Kitchen, M.D., 1010 Rialto Building, Kansas City, 6, Mo. Meetings last Friday of each month.

ST. LOUIS SOCIETY OF RADIOLOGISTS. *Secretary*, Edwin C. Ernst, M.D., 100 Beaumont Medical Bldg. Meets on fourth Wednesday, October to May.

Nebraska

NEBRASKA RADIOLOGICAL SOCIETY. *Secretary-Treasurer*, Ralph C. Moore, M.D., Nebraska Methodist Hospital, Omaha 3. Meets third Wednesday of each month at 6 P.M. in Omaha or Lincoln.

New England

NEW ENGLAND ROENTGEN RAY SOCIETY. *Secretary-Treasurer*, George Levene, M.D., Massachusetts Memorial Hospitals, Boston. Meets monthly on third Friday at Boston Medical Library.

New Hampshire

NEW HAMPSHIRE ROENTGEN SOCIETY. *Secretary-Treasurer*, Albert C. Johnston, M.D., Elliot Community Hospital, Keene. Meetings quarterly in Concord.

New Jersey

RADIOLOGICAL SOCIETY OF NEW JERSEY. *Secretary*, Raphael Pomeranz, M.D., 31 Lincoln Park, Newark 2. Meetings at Atlantic City at time of State Medical Society and midwinter in Newark.

New York

ASSOCIATED RADIOLOGISTS OF NEW YORK, INC. *Secretary*, William J. Francis, M.D., East Rockaway.

BROOKLYN ROENTGEN RAY SOCIETY. *Secretary-Treasurer*, Abraham H. Levy, M.D., 1354 Carroll St., Bklyn. 13. Meets fourth Tuesday of every month, October to April.

BUFFALO RADIOLOGICAL SOCIETY. *Secretary-Treasurer*, Mario C. Gian, M.D., 610 Niagara St., Buffalo 1. Meetings second Monday, October to May.

CENTRAL NEW YORK ROENTGEN SOCIETY. *Secretary-Treasurer*, Dwight V. Needham, M.D., 608 E. Genesee St., Syracuse 10. Meetings in January, May, and October.

LONG ISLAND RADIOLOGICAL SOCIETY. *Secretary*, Marcus Wiener, M.D., 1430 48th St., Brooklyn 19. Meetings fourth Thursday evening, October to May, at 8:45 P.M., in Kings County Medical Bldg.

NEW YORK ROENTGEN SOCIETY. *Secretary*, Wm. Snow, M.D., 941 Park Ave., New York 28.

QUEENS ROENTGEN RAY SOCIETY. *Secretary*, Jacob E. Goldstein, M.D., 88-29 163rd St., Jamaica 3. Meets fourth Monday of each month.

ROCHESTER ROENTGEN-RAY SOCIETY. *Secretary*, Murray P. George, M.D., 260 Crittenden Blvd. Rochester 7. Meets at Strong Memorial Hospital, third Monday, September through May.

North Carolina

RADIOLOGICAL SOCIETY OF NORTH CAROLINA. *Secretary-Treasurer*, James E. Hemphill, M.D., Professional Bldg., Charlotte 2. Meets in May and October.

North Dakota

NORTH DAKOTA RADIOLOGICAL SOCIETY. *Secretary*, Charles Heilman, M.D., 1338 Second St., N., Fargo.

Ohio

OHIO STATE RADIOLOGICAL SOCIETY. *Secretary-Treasurer*, Carroll Dundon, M.D., 2065 Adelbert Road, Cleveland 6. Next meeting at annual meeting of the State Medical Association.

CENTRAL OHIO RADIOLOGICAL SOCIETY. *Secretary*, Paul D. Meyer, M.D., Grant Hospital, Columbus. Meets second Thursday, October, December, February, April, and June, 6:30 P.M., Seneca Hotel, Columbus.

CINCINNATI RADIOLOGICAL SOCIETY. *Secretary*, Eugene L. Saenger, M.D., 735 Doctors Bldg., Cincinnati 2. Meets last Monday, September to May.

CLEVELAND RADIOLOGICAL SOCIETY. *Secretary-Treasurer*, George L. Sackett, M.D., 10515 Carnegie Ave., Cleveland 6. Meetings at 6:30 P.M. on fourth Monday, October to April, inclusive.

Oklahoma

OKLAHOMA STATE RADIOLOGICAL SOCIETY. *Secretary-Treasurer*, W. E. Brown, M.D., 21st and Xanthus, Tulsa 4. Meets in October, January, and May.

Oregon

OREGON RADIOLOGICAL SOCIETY. *Secretary-Treasurer*, Wm. Y. Burton, M.D., 242 Medical Arts Bldg., Portland 5. Meets monthly, on the second Wednesday, at 8:00 P.M., in the library of the University of Oregon Medical School.

Pacific Northwest

PACIFIC NORTHWEST RADIOLOGICAL SOCIETY. *Secretary-Treasurer*, Sydney J. Hawley, M.D., 1320 Madison St., Seattle 4, Wash. Meets annually in May.

Pennsylvania

PENNSYLVANIA RADIOLOGICAL SOCIETY. *Secretary-Treasurer*, James M. Converse, M.D., 416 Pine St., Williamsport 8. Meets annually.

PHILADELPHIA ROENTGEN RAY SOCIETY. *Secretary*, Arthur Finkelstein, M.D., Graduate Hospital, Philadelphia. Meets first Thursday of each month at 8:00 P.M., from October to May in Thomson Hall, College of Physicians, 21 S. 22d St.

PITTSBURGH ROENTGEN SOCIETY. *Secretary-Treasurer*, R. P. Meader, M.D., 4002 Jenkins Arcade, Pittsburgh 22. Meets second Wednesday of each month at 6:30 P.M., October to June.

Rocky Mountain States

ROCKY MOUNTAIN RADIOLOGICAL SOCIETY. *Secretary-Treasurer*, Maurice D. Frazer, M.D., Lincoln Clinic, Lincoln, Nebr.

South Carolina

SOUTH CAROLINA X-RAY SOCIETY. *Secretary-Treasurer*, Robert B. Taft, M.D., 103 Rutledge Ave., Charleston 16.

Tennessee

MEMPHIS ROENTGEN CLUB. Meetings second Tuesday of each month at University Center.

TENNESSEE RADIOLOGICAL SOCIETY. *Secretary-Treasurer*, J. Marsh Frére, M.D., 707 Walnut St., Chattanooga. Meets annually with State Medical Society in April.

Texas

DALLAS-FORT WORTH ROENTGEN STUDY CLUB. *Secretary*, X. R. Hyde, M.D., Medical Arts Bldg., Fort Worth 2. Meetings on third Monday of each month in Dallas in the odd months and in Fort Worth in the even months.

HOUSTON X-RAY CLUB. *Secretary*, Curtis H. Burge, M.D., 3020 San Jacinto, Houston 4. Meetings fourth Monday of each month.

TEXAS RADIOLOGICAL SOCIETY. *Secretary-Treasurer*, R. P. O'Bannon, M.D., 650 Fifth Ave., Fort Worth 4. Next meeting Jan. 7–8, 1949.

Utah

UTAH STATE RADIOLOGICAL SOCIETY. *Secretary-Treasurer*, M. Lowry Allen, M.D., Judge Bldg., Salt Lake City 1. Meets third Wednesday, January, March, May, September, November.

UNIVERSITY OF UTAH RADIOLOGICAL CONFERENCE. *Secretary*, Henry H. Lerner, M.D. Meets first and third Thursdays, September to June, inclusive, at Salt Lake County General Hospital.

Virginia

VIRGINIA RADIOLOGICAL SOCIETY. *Secretary*, P. B. Parsons, M.D., Norfolk General Hospital, Norfolk 7.

Washington

WASHINGTON STATE RADIOLOGICAL SOCIETY. *Secretary-Treasurer*, Homer V. Hartzell, M.D., 310 Stimson Bldg., Seattle 1. Meetings fourth Monday October through May, at College Club, Seattle.

Wisconsin

MILWAUKEE ROENTGEN RAY SOCIETY. *Secretary-Treasurer*, A. Melamed, M.D., 425 E. Wisconsin Ave., Milwaukee 2. Meets monthly on second Monday at the University Club.

RADIOLOGICAL SECTION OF THE WISCONSIN STATE MEDICAL SOCIETY. *Secretary*, S. R. Beatty, M.D., 185 Hazel St., Oshkosh. Two-day meeting in May and one day with State Medical Society, September.

UNIVERSITY OF WISCONSIN RADIOLOGICAL CONFERENCE. Meets first and third Thursdays 4 P.M., September to May, Service Memorial Institute, Madison 6.

Puerto Rico

ASOCIACIÓN PUERTORRIQUEÑA DE RADIOLOGÍA. *Secretary*, Jesús Rivera Otero, M.D., Box 3524, Santurce, Puerto Rico.

CANADA

CANADIAN ASSOCIATION OF RADIOLOGISTS. *Honorary Secretary-Treasurer*, E. M. Crawford, M.D., 2100 Marlowe Ave., Montreal 28, Quebec. Meetings in January and June.

LA SOCIÉTÉ CANADIENNE-FRANÇAISE D'ELECTROLOGIE ET DE RADIOLOGIE MÉDICALES. *General Secretary*, Origéne Dufresne, M.D., Institut du Radium, Montreal. Meets third Saturday each month.

CUBA

SOCIEDAD DE RADIOLOGÍA Y FISIOTERAPIA DE CUBA. Offices in Hospital Mercedes, Havana. Meets monthly.

MEXICO

SOCIEDAD MEXICANA DE RADIOLOGÍA Y FISIOTERAPIA. *General Secretary*, Dr. Dionisio Pérez Cosío, Marsella 11, México, D. F. Meetings first Monday of each month.

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ROENTGEN DIAGNOSIS

THE HEAD AND NECK

Intracranial Angiography via the Vertebral Artery. Preliminary Report of a New Technique. Stig Radner. Acta radiol. **28:** 838–842, Nov. 13, 1947.

During an anatomical investigation with another purpose in view, the author discovered, by chance, that the vertebral artery could be catheterized *via* the radial artery. Later, he was able to show that the vertebral artery of living beings may be catheterized in the same manner. After the injection of the radiopaque substance through the catheter, angiograms of the vertebral system may be made. This method has been used in only a few cases and further studies are planned.

Condylar Growth and Mandibular Deformities. Milton B. Engel and Allen G. Brodie. Surgery **22:** 976–992, December 1947.

Normal development of the mandible depends upon the synchronous co-ordination of the activities of various growth centers. Interference with any one of them may be expected to alter the orderly progression of development. Thus, growth arrest in the condyles is reflected in serious mandibular deformities.

The condylar growth center maintains its activity longer than most other centers in the head, persisting until at least the twentieth year. This provides the forward and downward vector for mandibular growth and contributes as well to increased width of the jaw. Disturbance of this area is not uncommon. It may occur as one of the sequelae of a mastoiditis or middle ear infection. Hematogenous infections or those which spread from the dental area may localize in the joint and lead to interference with chondral activity or to ankylosis and/or functional limitation. Similar effects sometimes proceed from trauma.

The authors studied 19 cases of condylar disturbances and present the details in tabular form. Roentgenographic studies were made by the Broadbent-Bolton cephalometric technic, and laminagraphic and routine films of the temporomandibular area were obtained in a number of cases. With unilateral arrest there is a deviation of the mandible to the involved side, the degree depending upon the time at which the condylar arrest occurred. Bilateral cases usually show a symmetric dysplasia.

The mandible that has become dysplastic through an early arrest will, if recovery occurs, follow the dysplastic pattern without any compensating acceleration, and the end-result will be an underdeveloped mandible. The growth disturbance is not corrected either by orthodontic treatment or by surgical procedures, though these may yield a degree of cosmetic improvement.

Surgical interference in the temporomandibular joint area should be undertaken most cautiously and only after serial observation of the patient has shown that growth has ceased. Otherwise, there is danger that an additional arrest will be superimposed on an already retarded growth center.

The authors present several methods of measuring the various angles formed by the mandible with the facial bones and sella-nasion plane. They also present methods of charting the growth and progression of the mandible so that it may be possible to determine the chronology, duration, and degree of arrest. Since the arrest is sometimes succeeded by a period of growth which is considerably decelerated, it is important to follow and chart these growth changes before determining the necessity of operation.

J. E. WHITELEATHER, M.D.

Hand-Christian-Schuller Disease of Mandible (Reticulo-endotheliosis). H. Goldin. South African M. J. **21:** 829–830, Nov. 8, 1947.

A case of Hand-Christian-Schüller disease of the mandible is presented, in which no other bones were found to be affected. The diagnosis was masked initially by the presence of what looked like a severe Vincent's angina, treatment for which was not effective. This case responded well to radical operation followed by x-ray therapy, and there had been no breakdown for a period of eighteen months postoperatively.

Intraocular Foreign Bodies. Wartime Experiences Applied to a Peacetime Problem. George M. Haik. J. A. M. A. **135:** 894–900, Dec. 6, 1947.

This article, which is little more than a restatement of generally accepted principles, stresses the limited application of military routine in the management of intraocular foreign bodies. It is suggested that all patients with eye injuries be placed in the recumbent position and kept in that position until the character and extent of the injury have been determined. First aid should be restricted to very simple measures such as covering the eye with a sterile pad, instructing the patient to remain quiet and warning him not to touch his eye under any circumstances. Emergency enucleation is seldom justified because sympathetic ophthalmia is a remote and calculable danger. The introduction of chemotherapeutic and antibiotic agents is one of the reasons why it was possible to delay the removal of intraocular foreign bodies in military practice and why comparable delay can be practised in civilian ophthalmology without fear of serious infection.

Although an intraocular foreign body is an emergency in the sense that it is abnormal and that abnormalities should not be permitted to endure any longer than necessary, military experience proved the wisdom of taking adequate time for accurate localization. General examination consisted of investigation by direct illumination, followed by the use of the loupe, the ophthalmoscope, and the slit lamp. In general the use of a magnet for diagnostic purposes was discouraged except as a last resort.

Military experience fully confirmed the value of roentgenologic localization of intraocular foreign bodies provided such procedure is carried out by specialized personnel, well versed in the refined technics considered essential to success. The Sweet method of localization was regarded as the most accurate single procedure available, although a combination of the Sweet technic with either the silver-ring method, the double-exposure method, or the lead-bead method was employed at times to good advantage. Precise roentgen localization was supplemented by use of the Berman or Carney locator.

The technic of extraction of intraocular foreign bodies depends upon the composition of the foreign material, its location, and the state of the eye. Pinpoint localization is far more essential than speed of extraction.

JOHN F. HOLT, M.D.
(University of Michigan)

THE CHEST

First Infection Pulmonary Tuberculosis in the Young Adult. Henry B. Zwerling. Acta radiol. **28:** 843–846, Nov. 13, 1947.

On the basis of several investigations, the author believes that much of the pulmonary tuberculosis in the young adult is of the first infection type and that this is probably frequently erroneously considered reinfection. Whether clinically first infection is more or less common than reinfection in the age group up to twenty to twenty-five years or beyond cannot be stated. It is probable that a significant number of cases of minimal pulmonary tuberculosis in the young adult and possibly in the older age groups are first infections.

The importance of distinguishing first infection and reinfection in the early small lesion is academic at this time, since in either instance the disease may become progressive. It is possible, however, that complete recovery from a first infection may be associated with increased resistance, such as is afforded with BCG vaccination.

Effect of Streptomycin Upon Pulmonary Tuberculosis Preliminary Report of a Cooperative Study of 223 Patients by the Army, Navy and Veterans Administration. Am. Rev. Tuberc. **56:** 485–507, December 1947.

Streptomycin Therapy in Progressive Pulmonary Tuberculosis. Preliminary Report of Clinical Investigation in 37 Patients. R. O. Canada, in collaboration with J. T. Pitkin, G. W. Hemstead, G. Jacobson, and Wylma Funk. Ibid. 508–533.

Streptomycin and Bed-Rest in the Treatment of Pulmonary Tuberculosis. Myron W. Fisher, George W. Fishburn, and John B. Wallace. Ibid. 534–539.

Streptomycin in the Treatment of Pulmonary Tuberculosis. Report of 15 Patients. Arnold Shamaskin, Louis C. Morris, Eugene J. Des Autels, Joseph Mindlin, James R. Zvetina, and Henry C. Sweany. Ibid. 540–551.

Pulmonary Tuberculosis Treated with Streptomycin. A Report of 20 Patients. W. A. Cassidy and Edward Dunner. Ibid. 552–564.

Streptomycin in the Treatment of Pulmonary Tuberculosis. A Therapeutic Review of 23 Patients. Christopher Parnall, Jr., Benjamin L. Brock, and Ralph E. Moyer. Ibid. 565–578.

Treatment of Pulmonary Tuberculosis with Streptomycin. Stanton T. Allison and J. M. N. Nilsson. Ibid. 579–588.

Streptomycin Therapy, with Special Reference to Pulmonary Tuberculosis. Nicholas D. D'Esopo and John E. Steinhaus. Ibid. 589–605.

The December 1947 issue of the *American Review of Tuberculosis* is devoted entirely to streptomycin therapy of tuberculosis and details the results of a cooperative study of 223 patients by the Army, Navy, and Veterans Administration. The first article in the series serves as an introduction for the seven which follow it and summarizes the results which are presented at more length in the subsequent papers. Also there is included a description of procedural details which were common to all of the seven studies and there are given the results of a review by an impartial committee which was appointed to assay the roentgenographic evidence which was disclosed.

Six stipulations were made with regard to the selection of cases for streptomycin therapy. Tubercle bacilli must have been recently recovered from the sputum or gastric contents before treatment was commenced. The presence of exudative lesions was insisted upon, and preference was expressed for minimal or moderately advanced disease. The patients must have been observed for at least sixty days prior to the initiation of treatment in order to establish the trend of the disease. Only patients whose disease was progressive or stationary by roentgenographic and clinical observations were to be included in the series. The patients were preferably to have been on complete bed-rest prior to streptomycin therapy. No pneumothorax was to be present on the side toward which treatment was primarily directed, nor was any collapse therapy to be introduced during treatment except in the case of acute contralateral spread. All patients were to be under forty-five years of age.

A daily dosage of 1.8 gm. of streptomycin was agreed upon. A number of laboratory procedures were required in view of the known potential ability of streptomycin to interfere with auditory and vestibular function, renal function, and blood formation. Stereoscopic and lateral x-ray films of the chest were to be taken immediately before streptomycin administration was commenced, single films being taken every two weeks during treatment, with stereoscopic films every month and films in lateral position as required.

The roentgenographic observations in most of the cases were examined by an impartial jury of nine phthisiologists appointed by the American Trudeau Society at the request of the Veterans Administration. None of these had been concerned with the investigation other than as a matter of general interest. The results of the various studies and of the observations by the jury are presented in a number of tables. One hundred and thirty-one of the 223 treated cases were reviewed by the jury and in addition the x-ray films of 88 untreated cases were similarly examined. Films from the two groups were not distinguishable from each other by any markings and were reviewed in random sequence. It was the judgment of the jury that little or no improvement occurred in the proliferative or fibrocavernous lesions of the treated patients. In this respect, the treated and untreated groups were similar. In the case of exudative lesions treated by streptomycin, 85 per cent of the lesions cleared somewhat during treatment and with a single exception the rest remained stationary. In the untreated cases the results were different—only 30 per cent of the exudative lesions improved on bed-rest during the 120-day period of observation. The judgment of the various investigators with respect to the degree of clearing was quite similar to that of the impartial jury. It is not maintained that the roentgenographic clearing is often marked or permanent. In fact, extension of lesions occurred in 8 per cent of cases toward the end of treatment and in 16 per cent during the first to fourth months following its completion. The incidence of sputum conversion was approximately 40 per cent.

The clinical changes during streptomycin therapy were as frequent in occurrence as the roentgenographic changes, and more impressive. Cough and the amount of sputum were almost constantly reduced. Fever, when it was present, was similarly affected, and more than 80 per cent of the patients gained an average in excess of 12 pounds in body weight.

In the opinion of the investigators, the role of streptomycin in the treatment of pulmonary tuberculosis lies in

the partial clearing of exudative lesions either as an end in itself or as a preliminary to the collapse measures which it often makes possible. Laboratory observations accompanying this study reaffirmed the two gross disadvantages of streptomycin therapy: the damage to the vestibular apparatus which it imposes and the development of a resistance by the tubercle bacilli, which in all probability makes the long continuation of treatment unprofitable. L. W. PAUL, M.D.

Follow-Up of Abnormal Pulmonary Findings Observed in Mass Chest X-Ray Surveys. Hilbert Mark. Minnesota Med. **30:** 1251–1252, December 1947.

The author mentions the following points as essential in the clinical evaluation of patients emerging from a mass survey with any question attached to their status:

"1. Definite diagnosis and whether the disease is communicable
"2. Extent of the disease and whether it is acute or chronic
"3. Prognosis and determination of therapeutic procedure
"4. If tuberculosis, disposition of the patient and whether his condition requires hospital or sanatorium care, or whether he may continue under local medical supervision."

The clinical study should include a history, physical examination, tuberculin and sputum tests, and further x-ray examination. A negative tuberculin test will rule out a chronic, long-standing pulmonary tuberculosis but not one of the more recent, more active, or especially fulminating varieties.

Sputum examination is properly stressed, but the point which is usually overlooked is omitted here also, *i.e.*, the importance of *repeated* sputum examinations. [The abstractor had a teacher who used to say that thirty attempts to find the bacillus constituted *at least a fair trial*. Another excellent teacher, who had done considerable work on the Loeffler antiformin method of sputum examination, centrifuged each specimen, fixing it to the slide with egg white. He was able repeatedly to demonstrate the bacillus when laboratories making the usual orthodox examination had turned in a series of negatives.]

Change or lack of change in the pulmonary lesions, demonstrable roentgenographically, will aid in determining whether the disease is acute or chronic, stable, retrogressive, or progressive.

A modification of Hilleboe and Holm's guide for the disposition of cases (Pub. Health Rep. **61:** 1759, 1946) is included. PERCY J. DELANO, M.D.

Limits of Photoroentgen Investigation. Hans Wespi. Schweiz. med. Wchnschr. **77:** 1171–1176, Nov. 8, 1947.

The author compared the results of photoroentgen study with fluoroscopy and 14 × 17-inch films in 849 school children between thirteen and eighteen years of age. He believes that the photoroentgen method gives no conclusive result as to either pulmonary or cardiac abnormalities. It is especially poor at demonstrating the hilar regions, and hilar tuberculosis, open apical tuberculosis, inactive parenchymal lesions, or the residua of pleurisy may be easily overlooked, although readily demonstrated by fluoroscopy. He concludes that for school children photoroentgenograms fail to meet the necessary requirements of a satisfactory screening method. He particularly emphasizes that this is in part due to the prevalence of hilar tuberculosis in childhood, and notes that he could demonstrate hilar changes 14 times as often by fluoroscopy as by photoroentgenograms. He therefore prefers fluoroscopy and tuberculin testing as the method of choice for tuberculosis surveys in this age group.

[The author appears to have compared a simple screening method with a relatively more complete workup, so that his comparison is not entirely fair. His conclusion that hilar changes are more readily found by fluoroscopy in the time usually devoted to examination in a mass survey is open to question. L. G. J.]

LEWIS G. JACOBS, M.D.

Noxious Gases and Bronchiectasis. Duane Carr, W. E. Denman, and E. F. Skinner. Dis. of Chest **13:** 596–601, November–December 1947.

The authors studied the pulmonary findings in patients who had worked in a government arsenal, loading shells with mustard gas, where they were exposed to varying amounts of the gas in the atmosphere. Exposure varied from three weeks to six or seven months. The histories follow a fairly uniform pattern. The acute phase begins with irritation of the conjunctival and respiratory mucous membrane, impaired vision, loss of taste and smell, epistaxis, sore throat, difficulty in swallowing, hoarseness, chest pain, retrosternal soreness, wheezing, and dyspnea. There may be anorexia, vomiting, weight loss, weakness, insomnia, and irritability. All symptoms, except those referable to the respiratory tract, disappear after removal from exposure to the atmosphere containing mustard gas. They are replaced by a chronic productive cough. As the condition progresses, the patient complains of dyspnea, fatigue, wheezing, night sweats, pain, and substernal soreness. Spontaneous remissions appeared in three cases; in all the others the symptoms were progressive.

Routine roentgenographic studies usually showed a normal appearance. In 11 there were evidences of emphysema. Interstitial fibrosis in the bases was rarely observed.

Bronchographic studies were done in 144 cases: in 14 there was no demonstrable change; 64 showed ragged and irregular bronchial walls, leading to a diagnosis of bronchitis; 41, including some of those with bronchitis, showed dilatation of terminal bronchioles or of two or three secondary bronchi, diagnosed as minimal bronchiectasis; 30 showed cylindrical dilatation of bronchi of moderate extent in two or three of the lobes or marked dilatation in one lobe, and in these a diagnosis of moderately advanced bronchiectasis was made; 16 showed far advanced bronchiectasis.

The authors believe that the pathological changes begin with an acute chemical irritation or burn of the bronchial mucosa, followed by inflammation, with a resulting loss of elasticity and ciliary action. Secondary infection supervenes, causing further damage, with erosion and destruction of elastic tissue.

HENRY K. TAYLOR, M.D.

Transitory Pulmonary Infiltration (Loeffler's Syndrome). Theodore L. Squier. Dis. of Chest **13:** 609–620, November–December 1947.

Three cases of transitory and migratory pulmonary infiltration which fulfill the criteria established by

Loeffler for the syndrome bearing his name are presented. In each instance, atopic rhinitis and asthma were present and sensitivity to multiple inhalant allergens was demonstrated. The first two cases exemplify the early, completely reversible stage generally regarded as characteristic of Loeffler's syndrome. In the third patient, although early infiltrations were of fleeting character, repeated attacks left increasing residual fibrosis and evidence of irreversible damage. It is believed that irreversible changes after allergic pulmonary infiltrations are especially apt to occur when so-called intrinsic or bacterial sensitivities are present.

Treatment of Acute Primary Atypical Pneumonia, Etiology Unknown. David Greer. South. M. J. **40:** 881–890, November 1947.

The author treated 45 children having primary atypical pneumonia with intravenous injection of pooled blood plasma. His observations are based upon this series of cases.

In the majority of instances there is no change in the chest demonstrable roentgenographically during the first twenty-four to forty-eight hours of the illness. The first changes noted are increased density of the hilar and usually the perihilar shadows in the affected area, from which there extends along the radiating bronchovascular structures definite soft lacy infiltration. The density of the hilar shadow becomes more marked, and soft mottled infiltration between the branches of the bronchial tree ensues. Seldom, however, is the infiltration sufficiently heavy completely to obscure the ribs, and outlines of the traversing bronchovascular structures can usually be distinguished. This is in direct contradistinction to the heavy shadow of a bacterial lobar pneumonia. The infiltration may extend outward, fan-wise, or as a pointed, roughly pyramidal structure having its base at the hilum. Seldom does it extend beyond the mid-line of the lung field, though occasionally the periphery of the lung will be invaded. In some cases the infiltration circumvents the entire hilum area on the affected side, involving the lung proper for only a short distance.

In 32 of the 45 children constituting the author's series, penicillin or a sulfonamide, or both, had been administered in adequate dosage from the onset of the illness for a period varying from three to ten days, without beneficial results, before plasma was given. In 13 children, pooled blood plasma intravenously was the only treatment. The unit of treatment in all but 8 cases was 250 c.c. of liquid plasma per injection. Twelve cases received two treatments on successive days. The remaining 33 received only one treatment each.

In every instance, after an adequate amount of plasma had been given, the harassing cough began to subside rapidly, and within twenty-four hours the child appeared to feel entirely well. In the majority, the physical findings in the chest disappeared completely within three to five days, though the abnormal x-ray findings in many persisted for a period of two to four weeks. The author is not certain that the lung condition characteristic of acute atypical pneumonia resolves any more rapidly after plasma therapy than following any other type of treatment, but the prompt termination of fever and rapid return to a state of normal well-being are most dramatic.

DANIEL WILNER, M.D.

Pulmonary Cavernous Hemangioma with Arteriovenous Fistula, Surgical Management: Case Report. J. Dewey Bisgard. Ann. Surg. **126:** 965–972, December 1947.

Hemangiomas of the lung are relatively rare as far as can be determined from reports in the literature and autopsy statistics. Rodes (J. A. M. A. **110:** 1914, 1938) is credited by the author with the first description of the condition as a clinical entity. Ten cases have since been recorded, including the one here described. In the present case and in 6 of those previously published, operation was done, and in all effected a cure.

These lesions are probably all congenital. They have been demonstrated in newborn infants, but often are not discovered until later in life, when the arteriovenous shunt, present in all of them, becomes large enough so that at least 25 per cent of the blood passes through it, producing cyanosis and other symptoms. Clubbing of the fingers, dyspnea on exertion, compensatory polycythemia, polyemia, and hyperhemoglobinemia are common findings. Hemoptysis, dizziness, fainting, headache, pain in the chest, cough, asthmatic paroxysms, fatigue, and syncope are sometimes noted. A continuous murmur over the pulmonary lesion is a common finding.

The diagnosis should be suspected with a history of cyanosis from childhood, clubbed fingers and toes, elevated red count without basophilic stippling and abnormal white cells, and other characteristic signs. Roentgenograms of the chest usually reveal one or more cylindrical areas of increased density in the lung. Bronchography will show these to have no connection with the bronchial tree, and under the fluoroscope they may often be seen to pulsate. Laminagraphy and kymography may help in the differential diagnosis.

Treatment consists in ablation of the vascular fistula. Ideally this should be accomplished without sacrifice of pulmonary tissue, but usually this is technically impossible and lobectomy or pneumonectomy must be done. In the author's case, the right lower lobe, containing two hemangiomas, was removed. The patient was a man of twenty-nine years who had had symptoms for over six years and had been completely incapacitated for three months. BERNARD S. KALAYJIAN, M.D.

Pulmonary Arteriovenous Aneurysm. A New Surgical Disease. William Law Watson. Surgery **22:** 919–929, December 1947.

Two cases of congenital pulmonary arteriovenous aneurysm are reported, bringing the total reported in the literature to 12 as of the date of submission of this paper (March 1947). [An additional case has since been reported, by Burchell and Clagett: Am. Heart J. **34:** 151, 1947, Abst. in Radiology **50:** 847, 1948—J. E. W.]

Shunting of blood directly from pulmonary artery to pulmonary vein results in low arterial oxygen saturation in the greater circulation. All changes are secondary to this condition. The aneurysms are presumed to be congenital and become symptom-producing through slow dilatation over many years.

Persistent cyanosis of the face, hands, and feet, clubbing of fingers and toes, a high red blood cell count, and high hemoglobin have been seen in most cases. Half the patients had exertional dyspnea. Hemorrhage, epileptiform seizures, bruit or heart murmur, cough, and persistent headache were occasionally observed.

Radiographic study shows a branching, lobulated

mass of uniform density in the lung field. In some cases, this was confirmed by tomographic and/or angiocardiographic studies.

Diagnosis may be established prior to operation if the possiblity of the condition is kept in mind. Six of the 12 patients were cured by surgery. The 6 untreated or medically treated cases either did not improve or died of complications. The latter include (1) spontaneous hemorrhage; (2) cerebral and coronary artery thrombosis due to slowed circulation time and increased red cell volume, and (3) a mild degree of invalidism due to the anoxemia.

Surgical procedures which have proved successful are pneumonectomy, lobectomy, and ligation of the feeder artery.

The author's first case, in a 27-year-old-marine, was found on routine separation radiography of the chest. The radiograph showed several circular and elliptical shadows in the right lower lobe, from 2 to 3.5 cm. in diameter. Laboratory studies were essentially normal. Aspiration biopsy and bronchoscopy did not add information. At operation, a soft, lobulated, pulsatile, compressible mass was found, fed by an aberrant artery arising from the descending aorta and apparently emptying into a pulmonary vein. After ligation of the artery, the mass was no longer palpable, and lobectomy was considered unnecessary. Check-up radiographs showed no change in the lung, but there were no symptoms and the patient returned to his usual occupation.

The second patient, a 21-year-old marine, had observed a duskiness of the skin and fingernails for one and one-half years and exertional dyspnea for six months. He complained also of headaches, weight loss of 30 pounds in two years, bleeding gums, and a prickly warm feeling over the entire body. An induction radiograph taken thirty-three months earlier showed a pulmonary lesion. Small hemangiomata were found on the left lower eyelid, the vermilion border of the lower lip, the tongue, the bed of one fingernail, and the palms of both hands. The heart was normal. The red blood cell count was 6,500,000, with hemoglobin 17 gm. The hematocrit reading was 58; the platelet count 110,000. Other findings were within limits of normal. Bronchoscopy and bronchography eliminated bronchial disease. During observation, the patient had a convulsion, with transient coma and paralysis of the left arm and leg. Angiocardiography showed a collection of wide vascular channels in the right lower lobe, in a racemose grouping. The pulmonary trunk and the left branch of the pulmonary artery were of normal size. The right branch was relatively large. Blood volume and oxygen saturation studies before and after operation are summarized. Right lower lobectomy was performed, and cyanosis cleared during the operation. Examination showed an arteriovenous aneurysm, with a multilobulated sinus connecting the pulmonary artery branch with a vein. The patient was considered cured.

J. E. WHITELEATHER, M.D.

Cardiokymography in Patients with Pneumothorax. Franco Fugazzola. Radiol. med. (Milan) **33:** 569–585, November 1947.

The author stresses the importance of maintaining complete apnea during kymography of patients with pneumothorax to avoid the extraneous movements of the cardiac border due to motion of the mediastinum during respiration. CESARE GIANTURCO, M.D.

An Unusual Aortic Aneurism Followed for Ten Years. W. G. Hartnett and C. S. Beatty. Dis. of Chest **13:** 627–630, November–December 1947.

The authors give the case history of a colored male who had had four hospital admissions between 1936 and 1946 because of cardiac decompensation. At the time of his first admission a large pulsating saccular aneurysm arising from the arch of the aorta was recognized fluoroscopically. By 1946 the aneurysm eroded and perforated the sternum and projected itself as a large horny tumor on the anterior chest wall, which ultimately ruptured. Three days prior to death, the horny tumor dropped off, and blood was observed oozing from the wall of the pulsating aneurysm.

HENRY K. TAYLOR, M.D.

THE DIGESTIVE SYSTEM

On Brachyoesophagus. Erik Wamberg. Acta paediat. **34:** 293–305, Nov. 20, 1947.

Brachyoesophagus is a term used to indicate a congenital short esophagus associated with a partial thoracic stomach. Approximately 70 cases have been previously reported, and the present paper is a report and discussion of 4 additional cases.

Roentgenographic findings were dilatation of the proximal esophagus, an area of stenosis, an inverted funnel-like distal esophagus, and an over-all shortening of the esophagus with a portion of the stomach above the diaphragm. The first case showed most of these features, and the second case, in a twin sister of the first patient, was similar. Both children had a history of periodic vomiting from the time of birth. Hematemesis was occasionally observed in the first case. The third case presented a similar history but occult blood was repeatedly found in the stools. Periodic vomiting with occasional hematemesis occurred in the fourth case.

The condition is interpreted as being the result of incomplete embryologic development. The diagnosis is made by x-ray study and esophagoscopy. In the latter procedure, a circular or funnel-shaped stenosis is encountered at the level of the seventh thoracic vertebra. Chronic esophagitis is found proximal to the stenosis and gastric mucosa is seen distal to it.

Treatment is symptomatic. Bouginage is considered dangerous and ineffective.

STANLEY H. MACHT, M.D.

Benign Ulcer of the Greater Curvature, with Case Report. Allen E. Hussar. Gastroenterology **9:** 778–788, December 1947.

A case of benign ulcer of the greater curvature of the stomach, the eighteenth authentic case to be recorded, is presented. The clinical diagnosis of a benign ulcer was based on the gastroscopic appearance of the lesion and the coexistence of an active duodenal ulcer. Except for the location, which was characteristic of a malignant lesion, the x-ray appearance did not furnish evidence denying its benign nature. The patient was followed four months before operation. During this time the rate of healing was slower than one would have expected from a peptic ulcer. A gastrectomy was performed, and the diagnosis of benign peptic ulcer of the greater curvature was confirmed by histologic examination.

[Another benign ulcer of the greater curvature is reported by Russell in the September issue of RADIOLOGY (**51:** 387, 1948)—ED.]

Amebiasis. Joseph H. Nicholson and Frank A. De Dominicis. New England J. Med. **237:** 799–805, Nov. 27, 1947.

This is a review of 60 cases of amebiasis treated in the Lovell General Hospital. The duration of symptoms varied from a few days to eleven years, and some of the patients were thought to have had an irritable colon. The most frequent symptom is diarrhea, which is sometimes bloody. The stool may be watery and brown and in a large percentage of cases contains mucus. Pain may be mild or severe and is usually located in the lower abdomen or about the umbilicus. It may be cramp-like and relieved by defecation. Loss of weight occurred in 11 patients, varying from 10 to 40 lb. Nausea, anorexia, and vomiting, with fatigability and dyspepsia were frequently found. Chills and fever occurred in those patients with hepatic abscesses.

In 47 cases in which proctoscopic examinations were done, there were mucosal hemorrhages. Seven cases showed typical sharply punched-out ulcer areas. Stool examination was positive in 46 cases. Barium enema examination of 28 patients showed spasticity in 2 and spasticity with irregular narrowing of the colon in 2. Cecal irregularity was noted in 4. Nine showed no x-ray changes.

Diagnosis of amebiasis requires extensive study. The history and proctologic examination together with study of the stool are the important features in making the diagnosis. X-ray examinations of the colon may be of help, but it is often difficult to distinguish an amebic granuloma from carcinoma. Bacillary dysentery and idiopathic ulcerative colitis may also present a differential problem. JOHN B. MCANENY, M.D.

Co-Existence of Pancreatic Carcinoma and Duodenal Ulcer: Report of Three Cases. Grayson F. Dashiell and Walter Lincoln Palmer. Gastroenterology **9:** 773–777, December 1947.

In a review of 90 cases of carcinoma of the pancreas, 3 instances of coexisting duodenal ulcer were found. These cases are reported in detail. In the first case the ulcer crater was demonstrated roentgenographically, but the cancer was unsuspected until jaundice appeared; in the second, the preoperative diagnosis was duodenal ulcer; in the third the ulcer was an incidental finding at operation, though re-examination of the films postoperatively showed a collection of barium in the apex of the duodenal bulb, presumably representing the ulcer crater. The coincidence is of interest, but is not considered significant statistically in view of the recognized frequency of duodenal ulcer in the population at large.

Roentgen Examination as an Aid in the Diagnosis of Islet Adenoma in the Pancreas. Olle Olsson. Acta radiol. **28:** 833–837, Nov. 13, 1947.

When an islet adenoma of the pancreas is suspected, the pancreatic bed should be examined roentgenographically according to the Engel-Lysholm method (Acta radiol. **15:** 635, 1934). The stomach is filled with gas by having the patient take an ordinary effervescing powder. Films are then taken with the rays directed horizontally in the prone and supine positions and one in the latter position in the anteroposterior direction as well. The region between the posterior wall of the stomach and the anterior border of the vertebral column is occupied by the pancreatic bed. When the pancreas is enlarged, this distance is increased. The distance is abnormal whenever it exceeds the width of one vertebral body.

A case is reported in which roentgenography according to this method revealed a local indentation in the posterior wall of the gas-filled stomach. Operation disclosed a small, well defined pancreatic tumor at the site of the indentation. Histologically this proved to be an islet adenoma. Postoperative films showed the impression in the posterior outline of the stomach to have disappeared. Roentgenograms are reproduced.

Acute Pancreatitis. An Experimental Study with Special Reference to X-ray Therapy. Tague C. Chisholm and Roy E. Seibel. Surg., Gynec. & Obst. **85:** 794–799, December 1947.

The authors induced pancreatic edema and necrosis in dogs by the method of Rich and Duff (Bull. Johns Hopkins Hosp. **58:** 212, 1936) and studied the serum amylase curves, the experiments covering periods of twelve hours and seven days. In the animals with edema only, the serum amylase was either approaching or had returned to normal at the end of the twelve-hour period; in those with severe necrosis a relatively high amylase level was maintained. This was found to be true also in the seven-day study.

Observations are also reported following periods of x-ray treatment to the normal pancreas; in a group of dogs which received a single dose of 90 r, the serum amylase levels showed a direct drop over a twelve-hour period, with return to or toward normal in two to five days. At autopsy every pancreas of this series showed only subsiding hyperemia. Another group receiving a single dose of 200 r displayed great variations in the serum amylase titers. At autopsy they had acute edema, petechiae, and tiny foci of fat necrosis. In a third group receiving three consecutive exposures, twenty-four hours apart, of 90 r each, uniform depression of serum amylase levels after the first treatment was observed, but with the second and third exposures amylase levels showed a steady rise.

Other observations are reported in dogs with acute experimental pancreatic necrosis followed immediately by a single x-ray treatment of 90 r. In these the serum amylase titers did not rise as high as in the original series without x-ray treatment, yet at autopsy moderately severe pancreatic necrosis was found.

In view of these experimental studies, the roentgen treatment of acute pancreatitis in man is considered, and the application of an appropriately small single dose is suggested to inhibit amylase enzyme production with minimal pancreatic tissue destruction.

JORGE DE LA FLOR, M.D.

Functional Disturbances of the Biliary Tract and Operative Cholangiography. Pablo L. Mirizzi. Prensa méd. argent. **34:** 2273–2275, Nov. 28, 1947.

This report on the value of operative cholangiography is based upon the experiences of seventeen years, during which the author examined at the operating table more than two thousand patients operated upon for biliary lithiasis. It is concluded that this method offers the surgeon a better guarantee than any other. Mirizzi disclaims any intention to exaggerate the intrinsic merits of this examination, but re-emphasizes the value of the procedure toward the perfection of which he has contributed so largely. JAMES T. CASE, M.D.

Pneumoperitoneum of Unknown Origin. Georges Pruvot, and Lucien Leger. J. de chir. **63:** 632, 1947 (Abst. in Prensa méd. argent. **35:** 753, 1948).

The observation of two cases of pneumoperitoneum in which examination of the abdomen, in one instance at laparotomy and in one at autopsy, did not reveal the cause of the gaseous accumulation, induced the authors to review the literature for similar cases.

Pneumoperitoneum is defined as "any accumulation of gas in the peritoneal cavity radiologically confirmed." The clinical picture is more generally acute, characterized by a dramatic beginning; abdominal distention with acute tympany; total disappearance of liver dullness; suspension of abdominal contractural reflexes; intestinal obstruction; oliguria; dyspnea, at times with cyanosis, and tachycardia. In half the cases the abdomen is painless. In some cases pain is present in the scapular region, a symptom of subphrenic irritation.

Of 53 reported cases, 31 were treated surgically, with 20 cures. Of the 22 patients not operated upon, 21 were cured; only 1 died, without peritoneal symptoms. It seems, therefore, that in these cases one should abstain from exploratory operations, and some authors have so recommended. In some instances, however, intervention permitted discovery of the perforation which had not been recognized. The authors declare that radiology should not be omitted, since its findings are decisive.

A question may be asked as to the origin of the gas. Some think it is of genital origin, and certain facts seem to corroborate this idea. Also there is the possibility of cystic pneumatosis with rupture of cystic vesicles, but this idea is not very satisfactory. Another possibility is microperforations, particularly in connection with gastric ulcers. Whatever the cause, pneumoperitoneum is a clinical entity, just the same as hydrops or pneumothorax. One should not consider it as a simple accessory sign. Not every pneumoperitoneum, however, means visceral perforation and a surgical emergency. JAMES T. CASE, M.D.

THE MUSCULOSKELETAL SYSTEM

Eosinophilic Granuloma of Bone, with Report of Two Cases. William M. Silliphant and Donald B. Hull. U. S. Nav. M. Bull. **47:** 1058–1066, November–December 1947.

This paper opens with a brief review of the literature, summarizing the early evolution of the diagnosis of eosinophilic granuloma. Sixty-five acceptable cases appear in the literature to February 1947.

The cause of the disease is as yet undetermined, but the authors believe that the most reasonable hypothesis is that it is an inflammatory response to an unknown agent. They are in accord with the prevailing view that eosinophilic granuloma, Letterer-Siwe's disease, and Hand-Schüller-Christian disease may well be different clinical-anatomic expressions of the same fundamental disorder.

Two cases are reported. In the first, the lesion was in the frontal bone. The patient responded well to surgery and postoperative irradiation. The second patient had multiple areas of involvement in the skull. These were curetted and roentgen therapy was given postoperatively. Five months later roentgenograms showed partial calcification of the lesions, but a new rarefied bone defect was present.

SYDNEY F. THOMAS, M.D.

Eosinophilic Granuloma of Bone. Edgar N. Weaver and John R. Carter. U. S. Nav. Med. Bull. **47:** 1066–1072, November–December 1947.

This is a single case report with an adequate review of the literature. The possible relationship to Letterer-Siwe's disease and Hand-Schüller-Christian disease is discussed. SYDNEY F. THOMAS, M.D.

Foreign Body Healing with Osteoplastic Reaction. K. Breinlinger. Schweiz. med. Wchnschr. **77:** 1179–1184, Nov. 8, 1947.

An 8-year-old boy had a piece of pencil in the tissues of the hand between the second and third metacarpals, which resulted in marked periosteal new bone formation on the shafts of both of these bones. Partial regression of this change followed removal of the foreign body. The pathology of this manifestation is discussed at length; the author is not sure whether it results from chemical irritation of the periosteum or mechanical irritation of new granulation tissue around the foreign body. LEWIS G. JACOBS, M.D.

Infantile Cortical Hyperostoses. Charlotte Fisk. J. Iowa State M. Soc. **37:** 529–532, December 1947.

An additional case of infantile cortical hyperostosis in a four-month-old boy is reported. The initial symptoms were soft-tissue swelling of the right forearm and right cheek and a pseudo-paralysis of the right forearm. Roentgenograms showed subperiosteal hyperplasia of the right ulna and radius and right mandible. There had been a continued recession of the swelling of the right forearm and a gradual disappearance of the cortical hyperplasia, and growth and development were progressing normally at the time of the report. It is thought that treatment has little effect on the course.

Köhler-Mouchet's Disease (Scaphoid Malacia), a Sequel to Industrial Trauma of the Wrist. Francisco Fernández Rozas. Prensa méd. argent. **34:** 2195–2212, Nov. 14, 1947.

Osteomalacia of the carpal scaphoid, described first by Köhler and later by Mouchet, is known also as aseptic necrosis or lacunar necrobiosis of the carpal scaphoid. It has also been designated as osteitis cystica (Preiser). The bone is involved in a neurovascular process marked by very particular anatomical-pathological-radiological aspects. The lesion may follow fractures which have healed by pseudo-arthrosis or may be secondary to trauma of various kinds (twisting, hyperextension, contusions, continuous minimal trauma in the carpal region, especially in certain professions).

After a lengthy and detailed discussion of symptoms and treatment, much space is given to medicolegal considerations. It is concluded that this disease has many points of similarity with the syndromes of Sudeck's and Kienböck's diseases, which are today recognized as due to disturbances of the sympathetics. Having once become established, this affection leads to irreparable sequelae which often justify the payment of high compensation. JAMES T. CASE, M.D.

Arachnodactylia. Thomas O. Dorrance. J. Pediat. **31:** 679–682, December 1947.

A case of arachnodactylia (Marfan's syndrome) in a six-year-old boy is described in detail. The patient presented elongation and attenuation of the bones, associated with muscular atrophy and an ocular anomaly

(iridodonesis). Roentgenograms of the hands and feet showed pronounced elongation of the metacarpals, metatarsals, and phalanges. The condition is believed to be due to a fault in the mesodermal cells of the embryo. About one-third of the reported cases are hereditary and familial. There is no satisfactory treatment.

STANLEY H. MACHT, M.D.

GYNECOLOGY AND OBSTETRICS

Hysterosalpingograms in Genital Tuberculosis in Women. Valdemar Madsen. Acta radiol. **28:** 812–823, Nov. 13, 1947.

The hysterosalpingograms in 20 cases of histologically verified and 22 cases of unverified but highly probable genital tuberculosis were studied. While there is no absolutely specific picture for tuberculous salpingitis, according to the author's observations the following features are strongly suggestive of a tuberculous lesion: (1) sactosalpinges without marked dilatation and (2) areas of calcification in the tubes or abdominal lymph nodes.

With these roentgenologic features in mind, several cases of genital tuberculosis were diagnosed which otherwise might not have been recognized. Among the 42 cases, more or less retort-shaped tubes, dilated slightly or not at all, were encountered in 29. Retention in more dilated sactosalpinges was seen in 8 cases, 3 of which also showed areas of calcification in the tubes; others showed calcified abdominal lymph nodes.

The combination of tubal retention of the contrast material and passage of the media into the peritoneal cavity was found in only one instance. Lack of tubal filling occurred in 4 cases, in 2 of which tuberculous endometritis was plainly evident. Tuberculous ascites was found in 1 patient.

In the 22 histologically unverified cases, the presence of salpingitis was established and for the above-mentioned reasons was thought most likely to be of a tuberculous nature. Seventeen of these patients gave a history of other manifestations of tuberculosis.

Further Experiences in the Roentgen Diagnosis of Tuberculous Salpingitis. W. Magnusson. Acta radiol. **28:** 824–832, Nov. 13, 1947.

In a previous study of the salpingograms in 12 cases of tuberculous salpingitis verified histologically (Acta radiol. **26:** 265, 1945. Abst. in Radiology **46:** 204, 1946), the author found that finely jagged and ragged contours with small lumen defects, and sometimes with abscess- and fistula-like extensions of the tubal lumen, constituted roentgen evidence of tuberculosis. On the basis of further experiences from 7 new cases and from a re-examination of all cases with tubal occlusion, a second type of salpingographic picture in tuberculous salpingitis is described, characterized by straight and rigid contours of the lumen and often by a pipe-like configuration of the tube. From the results of these examinations, it is concluded that a preoperative diagnosis of tuberculous salpingitis is possible in most cases of sterility due to this cause.

Nonfatal Pulmonary Embolism by Amniotic Fluid Contents, with Report of a Possible Case. Leo M. Seltzer and William Schuman. Am. J. Obst. & Gynec. **54:** 1038–1046, December 1947.

The authors report the case of a young woman of eighteen years who went into profound shock after delivery of her first child. They believe this may be an instance of pulmonary embolism by amniotic fluid contents, unique in that it did not terminate fatally. Eleven autopsy cases have appeared in the literature, but in no instance was a clinical diagnosis made either preceding or following death, the condition being invariably an unexpected necropsy finding. [In an addendum the authors mention 3 more recent cases reported by Gross and Benz (Surg., Gynec. & Obst. **85:** 315, 1947) after completion of the present paper.]

The physical findings in the authors' patient correspond to those reported by Steiner and Lushbaugh (J. A. M. A. **117:** 1245, 1340, 1941) in their autopsy series of 10 cases—cyanosis, dyspnea, fall in blood pressure, and râles due to pulmonary edema. This combination of findings, in the absence of cardiac disease, suggested a sudden pulmonary complication and, since no other cause was apparent, embolism by amniotic material was considered a possibility. The roentgen observations, showing almost complete clearing of the lungs in ninety-six hours, support this view, being in accord with experimental observations of the authors cited above. Those investigators injected suspensions of particulate matter from amniotic fluid intravenously in dogs and rabbits and found that in those animals surviving embolization the material was recognized with difficulty in the lungs after seven days, indicating the probability of its ultimate complete removal.

The following conditions were considered in the differential diagnosis in the authors' case and were ruled out: (1) postpartum hemorrhage; (2) pulmonary embolism from vascular thrombi; (3) eclampsia without convulsions as described by Teel *et al.* (Surg., Gynec. & Obst. **64:** 39, 1937); (4) aspiration of blood or stomach contents; (5) nitrous oxide asphyxia. Recovery was explained by a series of seemingly fortuitous events: (1) early diagnosis and therapy; (2) the patient's excellent physical condition; (3) the fact that she was under a general anesthetic during the embolic phenomena; (4) the apparent rapid absorption or at least complete removal of the particulate matter from the lung fields as evidenced roentgenologically. Two x-ray films of the chest are reproduced. The first (portable), made twelve hours postpartum, shows areas of increased density involving the second and third anterior interspaces on the left and the lower two-thirds of the right lung. Infarctions could not be ruled out. The second film, taken at ninety-six hours, shows complete clearing of both lung fields.

The etiology and contributing factors in this condition are discussed. The true incidence is not definitely established, since it is likely that sublethal and even subclinical forms exist. According to Steiner and Lushbaugh, the study of 72 obstetric deaths showed that pulmonary embolism by amniotic fluid was the most common cause in the period during labor and within the first nine hours thereafter. The interdiction of intravenous fluids or the very slow administration of whole blood in the presence of acute pulmonary edema, atropinization, morphine, and oxygen are the important therapeutic measures.

WILLIS MANGES, M.D.

THE BLOOD VESSELS

Peripheral Arteriography. LeRoy J. Kleinsasser Surgery **22:** 930–944, December 1947.

Peripheral arteriography with various radiopaque contrast media is a valuable procedure in the diagnosis

and treatment of arterial lesions. It is indicated for (1) visualization of aneurysms and fistulas and delineation of aneurysmal sacs; (2) early diagnosis of malignant bone lesions; (3) localization of arterial emboli; (4) determination of collateral circulation; (5) outlining of arterial injuries and determination of patency following injuries; (6) differential diagnosis of abscess and aneurysm; (7) determination of thrombosis of saccular arterial aneurysms; (8) determination of communications of parent vessels with vascular masses.

A rather extensive review of the literature on the use of different radiopaque materials is included. Diodrast, by transcutaneous injection, is recommended as the medium of choice for visualizing the peripheral arteries, though the dangers inherent in the method are not overlooked. A careful history concerning possible allergy and the conjunctival test for sensitivity are recommended as routine measures.

In the upper extremity, after insertion of a 19 gauge needle, arterial occlusion proximally is obtained with a sphygmomanometer cuff. The opaque material is allowed to progress to areas under study by allowing a small amount of blood to flow into the system. Appropriate radiographs are made.

In the lower extremity, occlusion is obtained by thumb pressure and injection is accomplished with the other hand. By timing the exposures, practically any portion of the arterial system may be visualized.

With arteriovenous aneurysms the vein may be erroneously entered, since it will be dilated and thickened and will contain arterial blood.

Vascular findings in malignant bone lesions, as described by Inclan (J. Bone & Joint Surg. **24:** 259, 1942. Abst. in Radiology **39:** 505, 1942) include filling in of the stroma of the new growth by numerous vessels, forming a bizarre network and outlining the tumor; premature appearance of a rich venous circulation; an increased arterial circulation distributed perpendicularly to the bone.

Complications were exceptional in the author's experience. Among those reported by various observers are (1) severe spasm and pain, which may result in thrombosis and ulceration, or aggravation of gangrene; (2) hematomas, extravasation, and local thromboses; (3) systemic reactions in all degrees, including death.

While arteriography has been considered unnecessary by many authors, Kleinsasser regards it as a simple and valuable adjunct to diagnosis and treatment.

The paper is illustrated by roentgenograms but the reproductions are rather poor.

J. E. WHITELEATHER, M.D.

Venography of the Lower Extremity: Its Clinical Significance and Technic. Fritz Jenny. Schweiz. med. Wchnschr. **77:** 1195–1198, Nov. 15, 1947.

The author reviews the history of venography from its origination by Berberich and Hirsch in 1923 (Klin. Wchnschr. **2:** 2226, 1923). He points out that venous thrombosis does not ordinarily result from a single plugging, but from the building up, in layers, of a thrombus, usually originating in the leg or foot. This permits the demonstration not only of the location, but also of the type of blockage. Often a large number of the veins are blocked, which contraindicates surgical excision. A most important use of venography is the investigation of obstructions following accidents; varices and trophic disturbances of the skin also are important indications for the procedure. In the case of varices secondary to deep blockage, venography will determine whether extirpation is feasible by demonstrating the status of the collateral and deep circulation. Although "deep" varices have been described, they are rare in the author's experience.

The use of "Roche" contrast medium is recommended—a 50 per cent solution for the leg and thigh and 70 per cent for the pelvic veins. The usual dose is 20 c.c. The venography may be indirect or direct; in the former the contrast medium is injected intra-arterially (usually in the femoral artery), and films are made after a short delay to permit the medium to reach the veins. This method has several disadvantages, one of the more serious being the extreme dilution of the contrast medium by blood. The direct method employs injection into a peripheral vein; for demonstration of the thigh and pelvic veins, no occlusive band is placed on the leg. For the pelvic veins, the injection may be made into the greater saphenous vein or a communicating varix, films being exposed forty seconds after injection. For the thigh veins, the time lag is reduced to five to twenty seconds. For the leg veins, the exposure is made during the injection, usually forty to eighty seconds before completion, and the medial marginal vein is recommended as the site of injection. The employment of stasis (*i.e.*, a tourniquet) leads to filling of all the veins rather than only those in the path of least resistance, and is recommended. Venography has not been employed in the foot.

Although complications, either local or general, are rare, their occasional occurrence suggests limiting this procedure to cases presenting definite indications.

LEWIS G. JACOBS, M.D.

Neurovascular Syndrome of the Arm Associated with Hypertrophied Subclavius Muscle. Report of a Case, Including Operative Treatment. Eugene E. Cliffton. Arch. Surg. **55:** 732–742, December 1947.

The authors report a case—apparently the first of its kind—of edema, cyanosis, weakness, pain, numbness, and tingling of the left hand following an auto accident in which the patient sustained a fracture of the left clavicle. He was able to abduct his arm only to 90°, and could not hold the arm out for more than a few seconds. An area of hypesthesia was found over the ulnar aspect of the wrist and hand, and over the fourth and fifth fingers. A venogram showed complete venous block with filling of the collateral circulation. At operation, the block was well demonstrated, It was due to pressure from a hypertrophied subclavius muscle. No thrombosis was found. The muscle was incised and sutured out of the way, with relief of the block and prompt and satisfactory return of function. It is noteworthy how closely the clinical and roentgen findings mimicked those of a post-thrombotic syndrome.

LEWIS G. JACOBS, M.D.

ECONOMICS

Economics of the Practice of Radiology. A Report Prepared by the American College of Radiology for the Council on Medical Service of the American Medical Association. Mac F. Cahal and C. E. Nyberg. J. A. M. A. **135:** 1078–1081, Dec. 20, 1947.

This paper gives current information concerning the economics of the practice of radiology, particularly hospital practice, as obtained from 880 practising radiologists in October 1946.

RADIOTHERAPY

Small-Scale Dosage Trials for Preparatory Studies in Radiological Treatment (Preliminary Report). D. Nicolaeff and R. Thoraeus. Acta radiol. **28:** 776–783, Nov. 13, 1947.

Before beginning radiotherapy, as a check of the calculations and a survey of dosage efficiency, trials of the planned treatment are made, using only small amounts of radiation. Small condenser chambers are placed singly, or suitably in pairs, at the centers, and in oblong fields also at the ends, of all the fields. In cases where a cavity is accessible, depth dose measurements may be carried out by introducing into the cavity a number of chambers contained in a tube of a suitable material. The chambers are placed one above the other from the closed end of the tube; all of the chambers mentioned remain in their respective positions during the course of the trial, thus recording the total amount of radiation received.

Small amounts of radiation (in most cases 50–100 r to each field), corresponding to the sensitivity of the condenser chambers and in suitable proportion to the skin doses of the treatment plan, are given to each field, one after the other. Before each irradiation an additional pair of chambers is placed at the center of the field which is to be irradiated and remains there only during that particular irradiation. These additional chambers thus record the dose directly given to each field. The complete treatment plan being accomplished on a small dosage scale, the chambers are removed and read, and an average for each pair calculated. The information thus obtained furnishes a survey of the dosage efficiency of the treatment plan before it is put into effect.

By means of dosage trials some cases of cross-fire irradiation of the thorax have been investigated, and certain general conclusions concerning the skin dose and percentage depth dose efficiency are drawn.

Distribution of Radiation in the Treatment of Carcinoma of the Cervix. Malcolm Donaldson. Acta radiol. **28:** 769–775, Nov. 13, 1947.

The author describes briefly a vaginal and uterine applicator designed by Neary and himself. This applicator has the following advantages: (1) When in position, its uterine and vaginal portions are fixed together to form one unit. (2) Treatment by this instrument gives in seventy-two hours a dose of radiation to the cervix at the external os of 10,000 r, at point *A* 8,000 r, and at point *B* 5,000 r over an area of 3 × 2 cm. (Point *A* is taken as the ureteric canal in the parametrium, *i.e.*, 2 cm. from the mid-line and 2 cm. above the vault of the vagina; Point *B* is 5 cm. from the mid-line and on the same plane as *A*.) (3) The applicator is fixed by means of a harness. Even if there were slight movement, which is extremely unlikely, the radium in the vagina is so far from the nearest tissue as to make the change in dose very slight indeed.

In the limited experience with this applicator, it has been found that the radium in the fundus of the uterus is too concentrated, having given rise in at least two cases to large necrotic abscesses and injury to the intestines from which the patients eventually succumbed. This defect is now being corrected.

The author states that the isodose curves with this applicator are far more advantageous than those with any previous instrument.

Experiences with Radiotherapy in Cancer of the Cervix and of the Corpus of the Uterus at the Radiumcenter in Odense. P. Jacoby. Acta radiol. **28:** 505–518, Nov. 13, 1947. **Treatment of Cancer of the Cervix at the Radiation Therapy Institute at Helsinki, 1937–42.** V. Kahanpää and J. O. Kankkunen. Ibid. pp. 519–530. (In German.) **A Clinical Review of 262 Cases of Cancer of Uterus.** L. Martindale. Ibid. pp. 531–541. **Summary of Results in the Radiation Treatment of Uterine Cervical Cancer. A Statistical Study of Volume 4 of the League of Nations "Annual Report on the Results of Radiotherapy in Cancer of the Uterine Cervix," edited by Prof. J. Heyman, Statement of 5 Year End-Results of 1,796 Patients Whose Treatment Began in 1933.** Harold Swanberg. Ibid. pp. 554–563.

Jacoby presents the results of radiological treatment of cancer of the cervix and of the corpus of the uterus at the Radium Center in Odense from 1928–41. Three hundred and seventy-three patients with cancer of the cervix were examined and 365 treated; 120 were free from evidence of disease after five years, with an absolute cure rate of 32.2 per cent and a relative cure rate of 32.9 per cent. Ninety-eight patients were admitted with cancer of the corpus, but only 92 were treated, 25 by the packing method of Heyman. The relative cure rate for the treated patients in this series is 38 per cent and for the clinically operable cases 66.5 per cent.

Kahanpää and Kankkunen's material comprises 524 cases of carcinoma of the cervix seen between 1937 and 1942. Only 35 per cent of the tumors were of Stages I and II. In 58 cases not even palliative treatment was attempted. The remaining 466 cases were treated according to the Stockholm method. The radium dose to the average uterus was 3,300 mg. hr. and in the vagina 4,710 mg. hr., making a total of 8,010 mg. hr. The calculated deep roentgen dose was 2,440 to each parametrium. The primary mortality was 2.8 ± 0.8 per cent; the five-year cure rate (absolute) was 31.9 ± 2.0 per cent. Relative five-year cure rates, by stages, were as follows: Stage I, 88 per cent; Stage II, 54 per cent; Stage III, 26 per cent; and Stage IV, 6 per cent. For all four stages, this figure was 35.8 ± 2.2 per cent. All treated cases were proved histologically. The prognosis depends, in general, on the stage of the cancer and the clinical picture. The histologic structure seems to have no special influence in this respect.

Martindale reviews 262 cases of cancer of the uterus. In 121 cases of primary cancer of the cervix treated by irradiation, the five-year survival rate was 36.3 per cent, with 100 per cent survival in Stage I cases, 55 per cent in Stage II, and 29.5 per cent in Stage III. None of the 16 patients with Stage IV cancer survived. Seventy-nine cases showed an over-all ten-year survival of 27.7 per cent. Radiotherapy was used in 33 cases of cancer of the corpus uteri. Eighteen of these patients survived five years (54.5 per cent); the ten-year survival rate was 30.3 per cent.

Swanberg reviews the League of Nation statistics on 1,796 patients with cancer of the uterine cervix treated at 18 radiotherapeutic centers in 8 countries beginning in 1933. Irradiation was used exclusively. The relative five-year rate for the entire group was 30.7 per cent (56.2 per cent, Stage I; 40.7 per cent, Stage II; 26.4 per cent, Stage III; 5.3 per cent, Stage IV).

The best results in all 18 radiotherapeutic centers, regardless of the number of patients treated, were secured

at the Radium Institute of the University of Paris, where 47.2 per cent of all patients treated were alive and free from cancer at the end of five years. The technic responsible for these excellent results consisted of combined internal (intracavitary) and external (transpelvic) irradiation (internal radium alone in Stage I). The internal radium treatment consisted of multiple, small milligram centers of heavily filtered radium distributed throughout the entire length of the uterine canal and width of the vaginal vault, slowly administered (five days time, averaging 8,000 milligram hours).

Methods to Reduce the Dangers of Radiotherapy in Cancer of the Uterus. D. Den Hoed. Acta radiol. **28:** 497–504, Nov. 13, 1947.

One of the causes of primary mortality in radiotherapy in uterine cancer is infection leading to sepsis. Cancer of the cervix usually shows ulceration in which, as a rule, pathogenic germs are present. The likelihood of infectious complications due to irradiation is increased by the manipulations in applying radium and by the decrease of the local resistance to inflammation following the high doses necessary to damage the cancer cells. It is a well known fact that heavily irradiated tissue is particularly sensitive to infection.

The chance of infection in a given case may be determined by checking the bactericidal power of the blood of the patient against her own vaginal flora, by means of the Ruge-Philip test. In 500 patients tested in this way the prognosis as to chance of infection was as follows: Group I, favorable, 55 per cent; Group II, somewhat doubtful, 20 per cent; Group III, doubtful, 7 per cent; and Group IV, bad, 18 per cent. Serious infectious complications were found to occur largely in Group IV. If, after application of radium, the patient had a slight reaction, subsequent treatment was conducted according to the bacteriologic findings. In patients in Group I, a wait-and-see policy was adopted; in Groups II and III, the therapist was on the alert; and in Group IV irradiation was immediately interrupted until the condition of the patient seemed to be normal again. Thus the most severe complications were avoided. The prophylactic use of the sulfa drugs proved helpful.

In order to prevent proctitis, a second important complication in the treatment of cancer of the cervix, the mode of irradiation has been modified to spare the rectal mucosa as much as possible by lowering the intravaginal radium dose and by applying a lead strip above the rectum in the front and back fields. Sometimes contact irradiation with a beam directed away from the rectum is used for bulky tumors. By thus sloughing down the bulk of the tumor, more room is gained to introduce the radium applicator and the gauze tampon. In this manner rectovaginal fistulas due to irradiation have been almost totally avoided.

Some Complicating Factors in the Radium Treatment of Carcinoma of the Cervix Uteri. Gilbert I. Strachan. Acta radiol. **28:** 545–553, Nov. 13, 1947.

The author considers certain side-aspects of radium treatment of carcinoma of the cervix, particularly those conditions which would contraindicate the application of radium and the complications which may follow its use.

Not every case of cervical carcinoma is suitable for the application of radium, at least not immediately, and the failure to appreciate this fact, usually because of insufficient investigation or lack of experience on the part of the surgeon, may markedly vitiate the result or may even precipitate disaster. The following are the main contraindications: (1) advanced emaciation and cachexia; (2) extensive anemia; (3) inflammatory pelvic lesions; (4) an extreme degree of pelvic extension of the growth; (5) fistula formation.

Two main points regarding the technic of radium application are emphasized. The first is the importance of finding the cervical canal so that it may be dilated and the intra-uterine tube of radium inserted, in order that the area involved by the cancer may be irradiated to the best advantage. In 28 per cent of the author's cases the cervical canal could not be found. The second point is the importance of efficient vaginal packing.

Various postoperative complications such as infection, pyometra, fistula formation, intestinal obstruction, and stricture formation are discussed.

Rectal Complications of Uterine Radium Therapy. A. Vachon and M. Dargent. Arch. d. mal. de l'app. digestif. September–October 1947. (Abst. in Prensa méd. argent. **35:** 751, 1948.)

The relative frequency and severity of rectal complications following radium therapy of uterine neoplasms led the authors to a rather extensive study of the subject. The first evidences generally appear shortly after application of radium in cancer of the cervix, consisting of rectal tenesmus and sometimes glairy, sometimes bloody, stools. Rectoscopic study shows the inflammatory aspect of the mucosal lesions. The symptoms rapidly recede and there follows a symptomless interval of from two to ten months, after which there commences a series of real rectal symptoms. These consist of rectal bleeding or a dysentery-like syndrome with colonic tenesmus and a bloody and glairy discharge. Exquisite pains projected into the perineum and radiating to the limbs tend to exhaust the patient. Rarely is there constipation. Examination shows lesions of hemorrhagic proctitis, ulceration of the anterior aspect of the rectum, stricture or rectovaginal fistula of slow evolution, with a tendency to chronicity. There may occur symptoms suggestive of perforation and peritonitis.

The diagnosis is somewhat uncertain, as none of the clinical symptoms is pathognomonic. The local examination suggests the idea of malignant disease. Biopsy can sometimes make the distinction.

The authors offer some suggestions for preventing the occurrence of these rectal complications. For vaginal irradiation, the radium tube should be so placed as to deliver the maximum intensity in the fundus of the lateral vaginal sacs. The intra-uterine applicator should be carefully fixed so that it cannot escape and come in contact with the posterior vaginal wall. Before radium treatment is begun, the integrity of the rectal ampulla should be carefully surveyed and one should avoid treating cases with parametrial infection. Penicillin should be freely used in these cases as a precautionary measure. Where hemorrhages have occurred, hemostatic irrigations should be employed. Sulfaguanidine may be given by mouth. JAMES T. CASE, M.D.

Rectal Injuries Following the Stockholm Method of Treatment of Cancer of the Cervix Uteri. Axel Ingelman-Sundberg. Acta radiol. **28:** 760–764, Nov. 13, 1947.

A study of 3,392 cases of carcinoma of the cervix uteri treated at the Radiumhemmet between 1914 and 1937,

by the Stockholm method of intracavitary radium application, revealed that rectal injuries occurred in 313. These injuries have generally been slight. Twenty-eight patients had subjective symptoms only, 178 slight local lesions, 91 ulceration, and in 16 rectovaginal fistulas developed.

The chief cause of the injuries is an overdosage of radium to the rectum, *i.e.*, more than 400 Imc. hours [milligram-hour per centimeter squared] (physic. approx. 3,300 r) measured with Sievert's condenser chambers, the centers of which have been applied about 7 mm. toward the lumen from the surface of the rectal mucosa. Syphilis and advanced age were found to be probable contributing factors.

The five-year cure rate among the patients suffering rectal injury was considerably greater than among the remaining patients (49.5 per cent ± 2.8 and 24.0 per cent ± 0.8 respectively). This is explained in part by the fact that in some of the advanced cases death ensues before rectal injury develops; also, the patients with rectal injury in general have smaller tumors than the other patients. Finally, the radium dose administered per volume unit of tumor has been greater in the rectal injury series, and this is believed to be the chief cause of the greater cure rate.

This paper is an abridgment of Supplement LXIV of Acta Radiologica, 1947.

A Dosimeter for Preventing Radiation Injuries to the Rectum During Treatment of Carcinoma of the Uterus with Radium. Harry Zilliacus. Acta radiol. **28:** 790–795, Nov. 13, 1947.

An apparatus is described which directly measures the intensity of gamma radiation in the rectum during gynecological radium treatment. The instrument consists of a rubber catheter in the tip of which an ionization chamber is situated, in which a 100-volt battery builds the electric field. In series with the dry cell battery and the ionization chamber is placed a resistance of 10^8 ohm. The potential across this resistance is measured with a vacuum-tube amplifier consisting of two vacuum tubes of the E1 6 type which are conducted in balance. The difference in the strength of the current in the anodes of the two vacuum tubes is measured with a 100 milliammeter. In order to obtain the best possible zero point constancy, the detecting vacuum tube for the anode potential is stabilized by a neon light. The heating current is taken from a 6-volt accumulator and the grid potential is delivered by a 9-volt dry cell battery. The sensitivity of the apparatus is such that 80 mg. of radium element, placed one centimeter away from the chamber, registers a tracing over the whole scale of the milliammeter.

Three Cases of Cancer of the Cervix During Advanced Pregnancy. Ekkert Petersen. Acta radiol. **28:** 542–544, Nov. 13, 1947. (In French.)

Three cases of cancer of the cervix seen during advanced pregnancy are presented. Treatment consisted of the local application of radium emanation. Parturitions were without unusual difficulty. Two of the patients had shown no evidence of recurrence in seven years. In neither case did menstruation cease, and one patient had a subsequent pregnancy; the children were developing normally. In the third case, the infant was born dead; there was an early recurrence of the tumor and the prognosis, when the patient was last seen, was considered hopeless.

Clinical and Experimental Observations in Radiotherapy in Functional Haemorrhage (A Preliminary Report). Hans Ludvig Kottmeier. Acta radiol. **28:** 736–759, Nov. 13, 1947.

The author applies the term functional bleeding to abnormal uterine hemorrhage in the absence of any lesion of the genital organs which might be responsible for this disorder. Before making a diagnosis of functional bleeding, it is of fundamental importance not only to obtain an accurate past history and particular information as to the type of bleeding present, but also to subject the patient to a careful medical and gynecologic survey, including intra-uterine exploration and diagnostic curettage. Histologic examination of the endometrium frequently is a valuable guide in determining whether the hemorrhage is ovulatory or anovulatory. This differentiation is of major importance in assessing the pathogenesis of this disorder and in planning the therapeutic program.

The indications for radiotherapy in preclimacteric and climacteric functional hemorrhage should be carefully evaluated. The younger the patient, the greater the need for critical consideration. The only conclusive indication for radiotherapy is hemorrhage which notably affects the general condition or the working capacity of the patient and which fails to respond to less drastic measures. The psyche of the patient and the risk of serious menopausal symptoms should not be overlooked.

The main purpose of radiotherapy in functional uterine hemorrhage is to induce the menopause, and the patient should be informed of this fact and of the symptoms which may develop. Radiotherapy should not be given unless a malignant tumor of the genital organs can be definitely ruled out. Menorrhagia does not exclude this possibility. Persistence or recurrence of irregular hemorrhage following radiotherapy in doses which should have a beneficial effect definitely points to the fact that indications for irradiation were not conclusive. As a rule, a patient of this type should not receive further radiotherapy and she should be followed closely for evidence of submucous myoma or neoplasm of the uterus.

Treatment of preclimacteric uterine hemorrhage at the Radiumhemmet consists either in roentgen irradiation of the ovaries or intra-uterine radium application, both methods having been used with excellent results. Heyman prefers intra-uterine radium (640 mg. hr with filtration equivalent to 1.0 mm. lead) to roentgen therapy for the following reasons: (*a*) Radium can and should be applied immediately after curettage. The treatment does not cause any serious discomfort to the patient and does not necessitate a prolonged stay in the hospital. (*b*) A lesser amount of normal tissue is irradiated by radium than by roentgen rays. (*c*) The effect of intra-uterine radium upon hemorrhage is more rapid; occasionally it may even be immediate.

Intra-uterine radium is contraindicated if the patient gives a history of an infectious process in the adnexa. Out of more than 400 patients who received intra-uterine radium application at the Radiumhemmet, salpingitis developed after treatment in only 2. No other complications occurred, and the patients did not have any complaints in connection with the treatment or afterward.

From 1913 to 1945, 772 patients were examined at the Radiumhemmet for preclimacteric or climacteric hemorrhage. No irradiation was used in 168 of these patients, either because the indications were not con-

vincing or because of the risk of severe menopausal symptoms. All but 2 of the 772 patients were either re-examined at the Radiumhemmet or followed by questionnaire. Satisfactory results were obtained in 96 to 100 per cent of the cases.

Special studies were undertaken in an attempt to explain the difference in time of occurrence of menopausal symptoms after radium irradiation and after treatment with roentgen rays. These are reported at some length. They included (1) microscopic examination of the ovaries in patients operated upon after having received intra-uterine radium application for preclimacteric functional hemorrhage; (2) comparison of the dose distribution over the ovary with roentgen irradiation and with intra-uterine radium application; (3) examination of urinary excretion of gonadotropic follicle-stimulating hormone; (4) examination of the urinary excretion of estrogenic hormone; (5) examination of the degree of response of the endometrium to estrogenic hormone; (6) examination of the effect of radium irradiation applied to one uterine cornu in rabbits, and comparison between the effect of roentgen rays and radium upon the uterus, ovaries, and pituitary in rabbits. It was shown that a considerably higher degree of ovarian function is maintained after intra-uterine radium application than after roentgen therapy, though hemorrhage often stops earlier after radium therapy. It is believed that the effect of radium therapy may be partly mediated through its action upon the arterioles in the uterine mucosa.

Wilms' Tumor (Embryoma of the Kidney). Henry K. Silver. J. Pediat. **31:** 643–650, December 1947.

This report is based on a series of 18 histologically proved cases of Wilms' tumor seen at the University of California Hospital between 1926 and 1944. Fifteen of the 18 patients were under six years of age at the time of the onset of the symptoms. Two patients were adults. Eleven of the patients were females. Hypertension occurred in 7 of the 8 patients in whom the blood pressure was recorded. No correlation was noted between age of onset, degree of hypertension, presence of hematuria, and the eventual outcome.

Treatment varied considerably. Since preoperative roentgen therapy was first used in 1939, all of the patients who are alive more than seven and one-half years (4 patients) were treated by nephrectomy alone or by nephrectomy plus postoperative irradiation. No patient survived without nephrectomy. Ten of the 13 patients on whom a nephrectomy was done are alive two and one-fourth to fifteen years after operation, a survival rate of 76.9 per cent. Of the 4 patients treated by nephrectomy alone, 3 are alive; of the 5 who had nephrectomy and postoperative irradiation, 3 are alive. All 4 patients who had preoperative irradiation plus nephrectomy and postoperative irradiation are still alive.

Treatment of Tuberous Angiomas in Young Children. Simone Laborde. Acta radiol. **28:** 723–735, Nov. 13, 1947. (In French.)

The employment of too high dosage in the roentgen and radium treatment of tuberous angiomas in young children may cause cutaneous lesions, retardation of growth of limbs, and injury to the nervous system. The author advocates minimum dosage, either by means of flat enameled containers which filter out the alpha rays and permit only the beta and gamma rays to reach the lesion, or by means of needles containing 1 or 2 mg. radium element (filtration 0.5 mm. platinum). The needles are used most often in voluminous angiomas.

The details of treatment are given in 10 cases, with photographs showing the results.

Cases of Haemangioma Vertebrae Roentgen Treated with Good Results. Sven Junghagen. Acta radiol. **28:** 715–722, Nov. 13, 1947.

Good results were obtained with roentgen therapy in 2 cases of hemangioma of the vertebrae. Both patients were young men and in both symptoms first appeared during heavy work. In the first case, not only were the vertebral bodies involved but also the arches and processes, and the destruction within these latter parts proceeded while the changes in the vertebral bodies remained stationary. This case presented primarily a picture of a radiculitis with pain, paresthesia, and a slight tendency to paresis. In the other patient a gibbus of the thoracic vertebrae appeared simultaneously with the onset of symptoms and grew in size without producing pain. Subsequent roentgen examination showed that this deformity was due to the destructive effects of the hemangioma localized to L-5, T-8 and T-9. The localization of the process in this case and the simultaneous presence of the static deformity led to a characteristic compression myelitis with a complete paraplegia.

In both cases treatment was chiefly by roentgen irradiation. In Case I, 16,040 r was given over a four-and-a-half-year period and in the second 9,260 r over a three-year period. The rays were hard filtered (tin) and were administered at a distance of 60 cm. and 50 cm., respectively, with 7 ma. and 190 kv. Treatments were given twice a day in the hope that the short intervals might further increase the effect. Improvement could be observed after each series of treatments in Case I, with only one relapse. In the second case improvement was first noticed almost two years after the beginning of treatment; at the time of the report, pain and paraplegia had to a large extent disappeared.

RADIOACTIVE ISOTOPES

Colloidal Gold Containing the Radioactive Isotope Au^{198} in the Selective Internal Radiation Therapy of Diseases of the Lymphoid System. C. W. Sheppard, James P. B. Goodell, and P. F. Hahn. J. Lab. & Clin. Med. **32:** 1437–1441, December 1947.

The release of radioactive isotopes from the chain-reacting uranium pile prompted the authors to consider the use of a different isotope in therapy, since Mn^{52} which they had previously used (South, M. J. **39:** 558, 562, 1946. Abst. in Radiology **48:** 561, 1947) was not available in therapeutic amounts from this source and a wide choice permitted a more favorable selection. It was required that the half-life, radiation, and specific activity be suitable (with absence of long-lived contaminants and toxic effects), that the production cost be low, and that the chemical and biological behavior be familiar. These requirements were best met by the radioactive isotope of gold, Au^{198}.

The half-life of Au^{198} is 2.73 days. This is ideal, in that the patient receives three-quarters of the radiation

from a given dose in about five and a half days, which gives the therapist a degree of control not possible with longer-lived isotopes. Gold was also acceptable because of its known biological behavior in colloidal suspensions.

The radiation emitted by gold consists of negative electrons with a maximum energy of 0.78 mev. and two gamma rays of an energy of 0.28 and 0.44 mev. Although a hard 2.5 mev. gamma ray is reported, it is not intense enough to make shielding difficult. Two inches of lead give ample protection for large amounts.

The reaction involved in production of the isotope is $_{79}Au^{197} + {}_{0}n^{1} \rightarrow {}_{79}Au^{198}$. The simultaneous factors of abundant parent isotope, high-capture cross section, and high neutron flux place this isotope in the high range of specific activities produced by the pile. It is this which permits such high and therefore therapeutically effective radiation doses to be administered in such small amounts of gold.

The cost is roughly two to five dollars per dose.

The chemical procedure in the preparation of radioactive gold for therapeutic use is simple. No radiochemical separation is required. It is necessary only to convert the metallic gold into a solution of gold chloride (probably aurochloric acid) and again to reduce this to metallic gold in an alkaline solution by adding ascorbic acid, preferably in the presence of gelatin. Intravenous administration is facilitated by the use of a saline infusion. The saline solution is run into the cubital vein in the usual manner and after satisfactory flow is established the sol is poured into the solution by the use of tongs.

The radioactivity of each dose is determined by measuring the gamma ray intensity at a distance of 1 meter using a Lauritsen electroscope, the measurements being made on an ordinary laboratory bench. Beta rays are shielded out by placing the container in a glass beaker. Pending establishment of accurate millicurie standards of radioactive gold, it was decided to adopt an empirical dosage unit. This was the amount of radioactive gold which produces a discharge rate of 0.5 small division per minute on the authors' electroscope.

This paper has been rather fully abstracted in order to demonstrate the amount of detail necessary in such an investigation. Clinical results are not included here. SYDNEY F. THOMAS, M.D.

Direct Infiltration of Radioactive Isotopes as a Means of Delivering Ionizing Radiation to Discrete Tissues. P. F. Hahn, J. P. B. Goodell, C. W. Sheppard, R. O. Cannon, and H. C. Francis. J. Lab. & Clin. Med. **32:** 1442–1453, December 1947.

The authors have found direct infiltration of insoluble radioactive colloidal sols of gold apparently a suitable method of delivering a given amount of radiation to a discrete mass of tissue under certain circumstances. X-rays can be delivered only from an external source. Thus in tumors originating in deep tissues of the body, considerable thickness of normal tissues must receive extensive irradiation in order to obtain effective dosage in the tumor. In the case of injection treatment with radioisotopes, on the other hand, the treatment is from within the tumor toward the normal tissue. Because of the relatively short path of the beta radiations, considerable effect can be produced in the tumor tissue with relatively little damage to the surrounding normal structures.

When radium needles or radon seeds are implanted in tissue in order to provide localized radiation, it is necessary to filter the alpha and beta emanations in order to avoid too intense radiation immediately about the needle or seed itself. Dependence is then placed upon the cross-fire gamma radiation to the affected tissue, but some irradiation of the adjacent normal structures cannot be avoided. In utilizing the radiation from colloidal sols directly infiltrated into the tumor tissue, many millions of "point sources" of radiation are involved in emitting beta rays diffusely throughout the injected volume of tissue. Since the mean free path of the beta ray is of the general order of 1.0 mm., any considerable irradiation of normal surrounding tissue is avoided. This is especially true in the case of Au^{198} or Au^{199}, since the gamma radiation is of little consequence in comparison to the intensive beta radiation. The gamma radiation, however, serves a very useful purpose in so far as it allows localization and determination of the concentration of the infiltrated material.

In general, the ultramicroscopic particles of gold remain *in situ* presumably because of their insolubility in body tissue fluids. As a result, a diffuse radiation is possible at any level of tissue ionization desired. With certain vascular tumors, however, the material will be carried away in the blood stream. Again, if the tumor is very friable, the fluid will seep out rapidly. Examples of both these difficulties are reported. To meet this problem, it has been suggested that use be made of the cauterizing properties of silver nitrate, using the isotope Ag^{111}. Preliminary investigations along this line are being conducted.

The method by which the gold sols are prepared is given, and 9 cases treated by the method are outlined, various complications and successes being recorded. The cases were chosen because they were totally inoperable and in a state where palliation only could be attempted. The study is purely a clinical one and no pathologic effects in the tumor itself are given.

SYDNEY F. THOMAS, M.D.

EFFECTS OF RADIATION

Microscopic Study of the Irradiated Larynx. V. Pricolo and F. Pizzetti. Radiol. med. (Milan) **33:** 587–596, November 1947.

The authors have studied microscopically 18 larynges which had been heavily irradiated prior to surgery. Of the 18 patients, 15 had received 6,000 r while the other 3 cases had received more than that. All were treated by the Coutard method.

The alterations found were: a slight amount of fibrosis, chondritis, and cartilaginous necrosis, and very little if any vascular change. The authors feel that such alterations are due more to the natural aging processes and to the vicinity of the tumors than to the irradiation. They state that roentgen therapy given according to the method of Coutard is without danger to the laryngeal tissue. CESARE GIANTURCO, M.D.

Effects of Radium on the Dentition. Martin A. Rushton. Am. J. Orthodontics **33:** 828–830, December 1947.

The author reports the case of a girl who had been treated for a cavernous hemangioma of the lips and

inside of the left cheek at the age of fifteen months by radium implantation and again at the age of three years and four months by application of a radium plaque (details of treatment not clear). At ten years of age, though the lesion appeared to be "considerably controlled," the lips were purplish and there was a cavernous hemangioma extending along the inner aspect of the cheek to the back of the mouth. There was a compressible swelling in the left submaxillary region and some prominent veins were present on the right side of the neck. The upper incisors and first permanent molars and the lower incisors and canines were erupted; many of them were badly decayed; their crowns were of normal size. Some teeth had been extracted. In roentgenograms all the anterior teeth were seen to have tapering, diminutive roots. Some of the unerupted teeth were small. All seemed to have very little roots. Some teeth were missing.

The author is of the opinion that, while the application of radium at the age of fifteen months could not affect the size of the crowns of the anterior teeth, in which hard-tissue formation had already begun, it might have damaged the tissue from which the roots were subsequently formed, the effect being more severe on the side nearest the radium. It might also have affected some of the tooth germs in which hard tissue formation had not yet begun, and especially those on the left side. The application of the radium plaque would probably have had little effect on the size of the crowns, but may have further stunted the development of the roots. Whether the complete absence of some of the teeth was due to radium absorption or extrusion or to some other cause such as extraction, it is not possible to say. It is also a question whether the early radium treatment was responsible for the caries. The author believes that it may have been so, either by causing imperfections in the tooth structure or bringing about a diminution of the salivary flow.

Effects of X-Ray Irradiation on the Development of Ovarian Tumors in Intrasplenic Grafts in Castrated Mice. Min Hsin Li, W. U. Gardner, and Henry S. Kaplan. J. Nat. Cancer Inst. **8:** 91–98, December 1947.

The paper presents results of experimental attempts to influence by x-irradiation, the development of tumors in ovaries grafted into spleens of castrated mice. The goal was to detect if possible any synergistic action of these two tumor-producing agents. The studies were as follows: (1) roentgen irradiation directed to the spleens; (2) irradiation to the pituitary glands of castrated mice bearing intrasplenic ovarian grafts; (3) irradiation of ovaries *in vitro*, prior to grafting into the spleens of other castrated mice; (4) grafting both of an *in vitro* irradiated ovary and an untreated ovary into the spleen in another series of mice.

Previous studies have shown that roentgen rays destroy ovocytes and prevent the formation of normal ovarian follicles in mice, and that irradiation is followed by irregular and prolonged estrus cycles, with probable reduction in the amount of estrogen produced. In many cases granulosa-cell tumors or luteomas develop if the irradiated animals survive a year or more. Such tumors also regularly occur in castrated mice 150 days or more after the intrasplenic implantation of ovarian grafts. These neoplasms are believed to be the result of excess hypophyseal gonadotropic hormones. It is considered possible that a similar mechanism is involved in the production of tumors by irradiation, the diminished estrogen secretion resulting in an environment of excess gonadotropic hormones produced by the hypophysis. It was partially to test this hypothesis that the experiments described in this paper were performed. It was hoped that the demonstration of synergism (or lack of synergism) of roentgen-rays and intrasplenic implantation would shed light on the mechanism by which irradiation acts in eliciting ovarian tumors in mice.

The results indicate no synergistic effect as compared with the previously reported incidence and induction time in non-irradiated intrasplenic ovarian grafts. Moreover, irradiation of the hypophysis did not inhibit the formation of the intrasplenic ovarian tumors.

Photomicrographs, together with detailed descriptions of the histopathological types of ovarian tumors, are included. EDWARD E. LEVINE, M.D.

Early Effect of X-rays on Ovaries of Normal and Adrenalectomized Rats. M. Ickowicz. Proc. Soc. Exper. Biol. & Med. **66:** 646–649, December 1947.

In a previous paper (Radiology **48:** 369, 1947) the author describes the changes occurring in the rat ovary during the first few hours after irradiation with x-rays. These alterations are characterized by the presence of numerous pyknotic nuclei of the follicular cells of the granular layer of the follicle. Further studies show that adrenalectomy inhibits the appearance of the pyknotic lesions in the rat ovary four hours after x-irradiation. The influence of adrenalectomy on the indirect effect of irradiation on the ovary has not yet been determined.

Influence of X-rays on Respiration of Nuclei of Fowl Erythrocytes. A. Back and L. Bloch-Frankenthal. Proc. Soc. Exper. Biol. & Med. **66:** 366–368, November 1947.

The effect of x-ray irradiation on the respiration of the nuclei of fowl erythrocytes was investigated by temporarily stimulating the nuclei with a dose of 500,000 to 1,500,000 r. This stimulation of nuclear respiration was more pronounced than that obtained with whole erythrocytes. The addition of hemolyzed blood or albumin to the suspension of nuclei before irradiation had a protective effect against the activating influence of x-rays.

Inhibition of Ribo- and Thymo-Nucleic Acid Synthesis in Tumour Tissue by Irradiation with X Rays. Barbara E. Holmes. Brit. J. Radiol. **20:** 450–453, November 1947.

The uptake of radioactive phosphorus in the thymo-nucleic acid fraction of Jensen rat sarcoma was markedly reduced by irradiation. The uptake in the ribo-nucleic acid fraction was also inhibited but to a less degree. If only one of the multiple tumors was irradiated, the same reduction in the nucleic acid fraction was observed in the untreated tumors.

Nembutal was found to be an unsuitable anesthetic in these studies, as it also caused a reduction in uptake of radioactive phosphorus in the thymo- and ribo-nucleic acid components of the cells.

SYDNEY J. HAWLEY, M.D.

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